MAYO AERO MEDICAL UNIT

STUDIES IN AVIATION MEDICINE

Volume III

Reports to Committee on
Aviation Medicine
NRC, OSRD

MAYO AERO MEDICAL UNIT

STUDIES IN AVIATION MEDICINE

Carried out with the assistance of the

NATIONAL RESEARCH COUNCIL, DIVISION OF MEDICAL SCIENCES

acting for the

COMMITTEE ON MEDICAL RESEARCH
of the
OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT

COMMITTEE ON AVIATION MEDICINE

With the cooperation of the

UNITED STATES ARMY AIR FORCES, MATERIEL COMMAND, WRIGHT FIELD.

Responsible Investigators: Walter M. Boothby, E. J. Baldes and C. F. Code

aided by many associates.

In Six Volumes

These reports, originally in "restricted" classification, have been declassified and all are now "open."

VOLUME 3: REPORTS TO COMMITTEE ON AVIATION MEDICINE

Mayo Clinic and Mayo Foundation for
Medical Education and Research,
University of Minnesota

Rochester, Minnesota
1940 - 1945

COMMITTEE ON WAR MEDICINE, MAYO ASSOCIATES
representing the
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STAFF OF THE MAYO AERO MEDICAL UNIT

Responsible Investigators

High Altitude Laboratory: Walter M. Boothby, Chairman. Member of the Subcommittee on Oxygen and Anoxia of the Committee on Aviation Medicine, National Research Council.

Acceleration Laboratory:** E.J. Baldes, Vice Chairman. Member of the Subcommittee on Acceleration of the Committee on Aviation Medicine, National Research Council.
C.F. Code, Secretary. Member of the Subcommittee on Decompression Sickness of the Committee on Aviation Medicine, National Research Council.

Investigators

Staff of the Mayo Clinic and Mayo Foundation: (Full time) E.J. Baldes, J.B. Bateman, W.M. Boothby, A.H. Bulbulian, C.F. Code, H.F. Helmholz, Jr., E.H. Lambert, W.R. Lovelace, II and E.H. Wood. (Part time) J.D. Akerman,*** J. Berkson, H.B. Burchell, P.L. Cusick, H.E. Essex, G.A. Hallenbeck, W.W. Heyerdale, H.C. Hinshaw, J. Piccard,*** M.H. Power, C. Sheard, J.H. Tillisch, M.N. Walsh and M.M.D. Williams.

Fellows of the Mayo Foundation: R. Bratt, B.P. Cunningham, W.H. Dearing, E.W. Erickson, N.E. Erickson, J.H. Flinn, J.K. Keeley, J. Pratt, F.J. Robinson, R.F. Rushmer, G.F. Schmidt, H.C. Shands, H.A. Smedal, A.R. Sweeney, A. Uihlein, R. Wilder, Jr., J. Wilson and K.G. Wilson.

Officer assigned by the Air Transport Command of the Army Air Forces: K.R. Bailey, pilot.

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Officers assigned by the Navy: W. Davidson and D.W. Gressley.

Officers sent by other governments: J.R. Delucchi, Argentina, and R.T. Prieto, Mexico.

Other investigators: M. Burcham, C.J. Clark, M.A. Crispin, R.E. Jones, G. Knowlton, H. Lamport, C.A. Lindbergh, C.A. Maaske, G.L. Maison, A. Reed and R.E. Sturm.

Technicians

High Altitude Laboratory: Henrietta Cranston, Lucille Cronin, Ruth Knutson, Eleanor Larson and Rita Schmelzer; Margaret Jackson (from Wright Field).

Acceleration Laboratory: L. Coffey, R. Engstrom, H. Haglund and A. Porter; Ruth Bingham, Velma Chapman, Marjorie Clark, Wanda Hampel and Marguerite Koelsch.

Secretaries

Evelyn Cassidy, Esther Fyrand, Marian Jenkins and Ethel Leitzen.

* Before going into military service.

** The major reports of the Acceleration Laboratory will be published shortly in the monograph entitled "The Effects of Acceleration and Their Amelioration," edited by the Subcommittee on Acceleration of the Committee on Aviation Medicine of the National Research Council.

*** From the Department of Aeronautical Engineering, University of Minnesota.

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NATIONAL RESEARCH COUNCIL, DIVISION OF MEDICAL SCIENCES

acting for the

COMMITTEE ON MEDICAL RESEARCH
of the
Office of Scientific Research and Development

COMMITTEE ON AVIATION MEDICINE

RESTRICTED

Report No. 163
Date June 1943

COMPARISON OF ALVEOLAR OXYGEN PRESSURES, OXIMETER READINGS AND PERCENTAGE OF SATURATION OF HEMOGLOBIN. From the Mayo Aero Medical Unit, Rochester, Minnesota, by Walter M. Boothby, Responsible Investigator, and F. J. Robinson, First Assistant

SUMMARY

I. The oximeter used at the Mayo Aero Medical Unit was a modification by E. D. Coleman of the Millikan oximeter known as Coleman Model 17. The manufacturer's calibration was checked by (1) reading the per cent saturation of the hemoglobin directly from the oximeter scale and (2) practically simultaneously obtaining a sample of arterial blood for analysis of its oxygen content and after equilibration for its oxygen capacity in the manometric apparatus of Van Slyke and Neill. The correlation is shown in the first chart.

II. The special oximeter thus calibrated was used to study the relationship between the oximeter readings of the percentage saturation of the hemoglobin and the partial pressure of oxygen in the alveolar air. A total of 572 observations were obtained and the data is presented in a series of seven charts. The data shows that on the average the percentage saturation of hemoglobin is in excellent agreement with the partial pressure of oxygen in the alveolar air whether the subject is at rest or at work or whether the alveolar air was obtained by the Haldane-Priestley or bag-rebreathing method. The plots of the individual observations show a considerable scatter but a variability after all surprisingly small considering the possibilities of error both in the oximeter and in obtaining a corresponding alveolar oxygen pressure

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REPORT

I. In order to check the manufacturer's calibration of a Millikan oximeter modified by E. D. Coleman, known as the Coleman Model 17 (no. 5769), Code, Power, Sturm and Wood of the Mayo Aero Medical Unit carried out in October 1942 a series of fifteen experiments in which (1) they read the per cent saturation of the hemoglobin directly from the oximeter scale and (2) practically simultaneously obtained a sample of arterial blood from the anticubital artery. The blood was collected in a 20 c.c. syringe containing heparin and a minimum amount of mineral oil. Duplicate samples were immediately analyzed for their oxygen content in the manometric apparatus of Van Slyke and Neill. The remainder of the blood was kept (not exceeding two hours) at low temperature in ice water until time was available for determination of its oxygen capacity.

This data is reproduced in chart III-8A and shows that there is excellent correlation between the percentage saturation of the hemoglobin read off directly on this particular oximeter (manipulated under ideal conditions by trained personnel) and as determined by careful chemical analyses. Only one of the determinations falls just outside the range of ± 5 percentage points and ten out of the fifteen observations are within ± 2 percentage points.

II. The present investigation in which 572 observations were made have been confined to determing whether this same oximeter which showed such close correlations with actual blood gas determinations would show a correlation with the partial pressure of oxygen in the alveolar air.

The averages of the percentage saturations of the hemoglobin obtained at the different elevations as read from the oximeter fall for the most part within 1 or 2 percentage points of Dill's oxygen dissociation curve (pH 7.4) when plotted against the average of the partial pressure of oxygen in the alveoli whether at rest or at work and whether the alveolar air was obtained by the Haldane or by the bag-rebreathing method. However, the individual observations of the different series show a considerable and apparently accidental scatter. This scatter is sufficiently great to render an individual observation rather doubtful as a criterion of a subject's safety at simulated high altitudes in chamber work. On the other hand, the oximeter is a valuable instrument for determining a large number of observations which can be averaged to give a reliable mean.

The vagaries of the oximeter itself and the difficulty of obtaining alveolar air samples that truly represent a mean value of the oxygen partial pressure are complicating factors. At low altitudes there is the added difficulty due to the

fact that the dissociation curve is approaching its asymptote and that therefore accidental high readings are less likely to occur and compensate for the accidental low readings due in part to blood being exposed to oxygen in some of the deeper alveoli which is considerably below the average that would be obtained in an alveolar air sample. Finally the oximeter does not reflect the influence of alterations in pH on the dissociation curve of hemoglobin; however, it is unlikely that in the tissue capillaries of the ear the change in pH will be sufficient to affect to more than a slight degree the dissociation curve, at least for two or three hours of moderate anoxia.

There are two ways of setting the oximeter. The method probably most generally used is to assume that approximately the oxyhemoglobin is 95 per cent saturated when breathing room air. This assumption is not necessarily true; therefore it is better to have the subject breathe oxygen and set the oximeter at 100 per cent. In our early experiments we used the first method as we hardly anticipated that the averages would be sufficiently consistent to indicate that as a rule if the oximeter was set at 100 per cent on oxygen that when the subject subsequently breathed air it would indicate 96 to 98 per cent saturation with an average of 97 per cent. (See chart III-10A). In consequence we now always set the instrument on 100 per cent with the subject breathing oxygen.

As there are at times fluctuations in the oximeter readings of 2 to 4 percentage points we finally adopted the routine of having the technician record the exact reading of the oximeter either at 10 or 15 second intervals, thus approximating a recording instrument. All results obtained were included except occasionally when there were technical difficulties in the oximeter, especially when subject was exercising, as evidenced by extreme fluctuations from static electricity (in spite of attempted grounding) or a consistent drift in readings so that a control observation with the subject breathing oxygen was definitely off. The disturbing influence of static was minimized and usually eliminated by liberally sprinkling the carpet-rug on the floor of the chamber with water to increase the humidity when the room air bleeding into the chamber was very dry as in cold winter weather.

While an indirect method like the oximeter does not justify the conclusion that as a rule in young individuals the arterial blood is normally saturated to 97 per cent when breathing air, yet it is sufficiently consistent to indicate that direct methods for determination of both the percentage saturation and also the oxygen tension in arterial blood should be used to carefully determine this point.

III. Two distinct methods of obtaining alveolar air samples in the low pressure chamber at ground level (1,000 feet) and at different altitudes have been used, both at sitting rest and at light work.

A. The standard method of obtaining an alveolar air sample is that commonly known as the Haldane and Priestley method: the alveolar air is obtained by giving a quick, deep expiration into a 3/4 inch hose (with simple mouth piece) about 4 feet long; after the expiration the subject closes the mouth end of the tube with his tongue and the sample of the last part of breath drawn out into a mercury sampling tube. To render the method slightly simpler we use a special valve which is snapped at end of expiration to close off the sampling tube and so constructed that during the expiration the entire tube on the inside is smooth and contains no pockets.

B. To obtain what might be a better average alveolar air a new method of collection was devised: a 5 liter rubber bag was attached to the same valve mentioned above instead of the long hose tube; the subject expired quickly and deeply into the

completely empty bag, exactly as in the Haldane-Priestley method and then inhaled two or three times followed by complete expiration. In one series this was done for three expirations into bag and two inhalations from bag, closing the valve at end of third expiration, and in another series there were three inhalations and four expirations. No significant difference was found (chart III-10C) between 3 and 4 expirations; therefore we will in the future standardize on 3 expirations.

IV. The data thus obtained is presented in a series of charts which are in the main self-explanatory and therefore need little additional description.

A. In chart III-10A are shown 259 observations of essentially simultaneous oximeter readings and alveolar oxygen pressures averaged for altitude. The oximeter was read several times during the minute before collecting the alveolar air samples by the Haldane-Priestley method. In 202 of these observations the oximeter was arbitrarily set at 95 per cent saturation with the subject breathing air at ground level (1,000 feet) while in 57 observations the oximeter was set at 100 per cent with the subject breathing oxygen, so the oximeter in the latter series read on the average 97 per cent when the subject returned to breathing air at ground level.

It is to be noted that the average figures plot very satisfactorily along the oxygen dissociation curve of Dill for a pH of 7.4 and it appears that in normal subjects the hemoglobin is on the average 97 per cent and not 95 per cent saturated when the subject is breathing air at or near sea level.

B. Chart III-10B shows the values for 259 individual observations which were expressed as averages in chart III-10A. There is, as can be seen, a very definite scatter of the individual observations which is smoothed out in the averages of the preceding chart. Chart III-10Ba gives possibly a clearer picture of the correlation of those observations of chart III-10B which were made with the oximeter set on oxygen.

C. Chart III-10C shows the average values of 106 observations. Of these, 58 observations were obtained by the technic of exhaling deeply three times into (inhaling twice from) a 5 liter bag and 48 observations by exhaling deeply four times into (inhaling three times from) the bag.

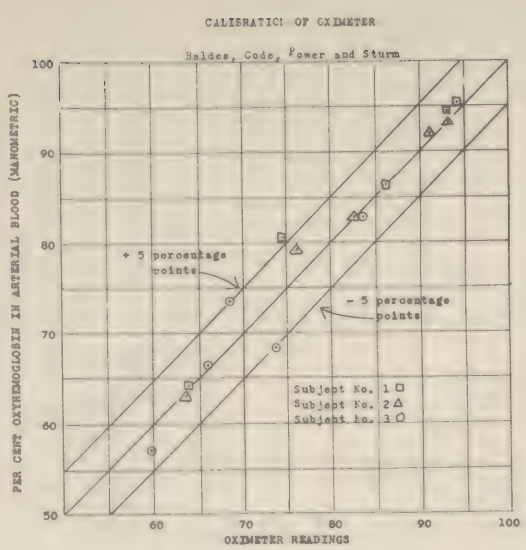
Note that values for both the three breath and the four breath series are practically identical and when plotted show very excellent correlation with Dill's curve for dissociation of oxyhemoglobin at pH of 7.4 although there is a slight indication that there is a tendency for the data to fall somewhat to the left of the dissociation curves at 12,000 and 15,000 feet, possibly from the effects of the increased ventilation caused by the anoxia which always occurs at these altitudes.

D. Chart III-10D shows the individual observations comprising the average values given in chart III-10C. This figure shows a slightly lesser spread of the individual observations obtained by the bag-rebreathing method than those obtained by the Haldane-Priestley method shown in chart III-10B. Chart III-10Da gives possibly a clearer picture of the degree of correlation of the data shown in chart III-10D.

E. In chart III-10E are shown the average values for altitude of 207 determinations of which at sitting rest 40 were made by the Haldane-Priestley method and 40 by the bag-rebreathing method (using three breaths); at work 63 were made by the Haldane-Priestley method, and 64 by the bag-rebreathing method. The work was accomplished by having the subject step up on a 5 inch step 16 times per minute in time with a metronome set at 80 per minute to obtain 5 beats to alternate legs used for elevation by introducing an extra non-elevating step on the floor.

The results show a very good correlation both at rest and at work by both methods of collecting alveolar air samples with Dill's dissociation curve (pH 7.4). The experiments at work showed a lower degree of percentage saturation of the hemoglobin by the oximeter than did those at rest but there was a corresponding decrease in the partial pressure of oxygen in the alveolar air by both alveolar air methods so that the experiments at work as well as those at rest agree closely with Dill's dissociation curve at pH 7.4.

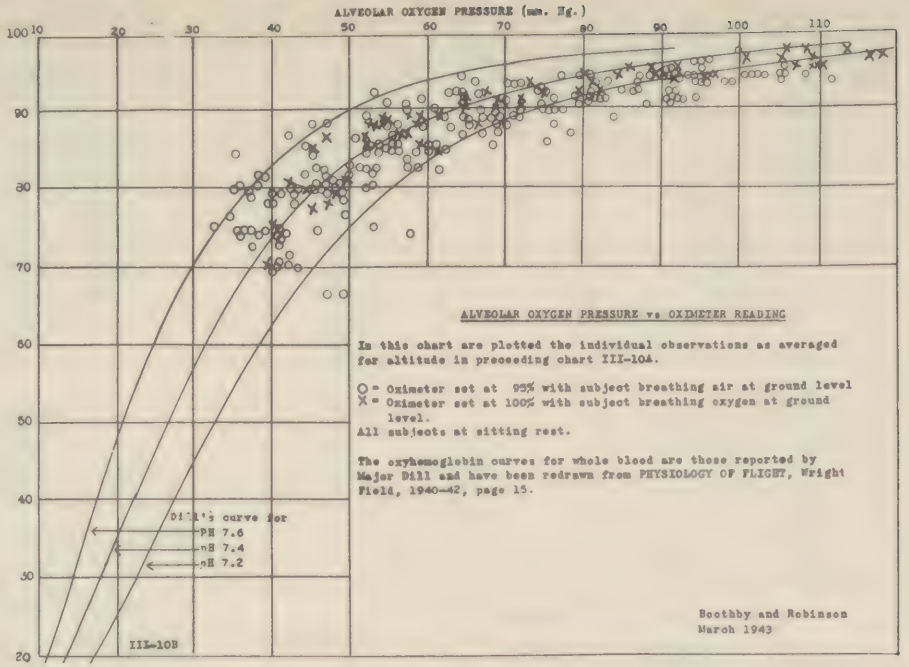
COMPARISON OF OXIMETER READINGS AND ALVEOLAR OXYGEN PRESSURES



This chart shows the calibration data on the oximeter used in this laboratory (Coleman Model 17, 5769) obtained by analysis of the oxygen capacity and content of the arterial blood by the manometric technic of Van Slyke and Neill. Subjects at lying rest.

Boothby and Robinson March, 1943.

III -8A



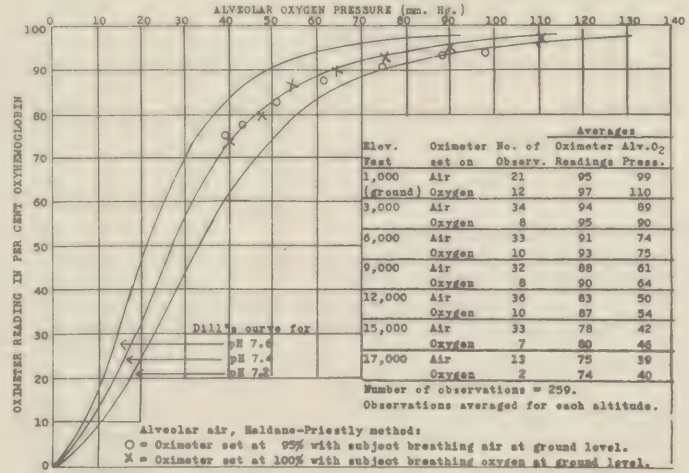
ALVEOLAR OXYGEN PRESSURE vs OXIMETER READING

In this chart are plotted the individual observations as averaged for altitude in preceeding chart III-10A.

○ = Oximeter set at 95% with subject breathing air at ground level
X = Oximeter set at 100% with subject breathing oxygen at ground level.
All subjects at sitting rest.

The oxyhemoglobin curves for whole blood are those reported by Major Dill and have been redrawn from PHYSIOLOGY OF FLIGHT, Wright Field, 1940-42, page 15.

Boothby and Robinson
March 1943



Elev. Feet	Oximeter set on	No. of Observ.	Averages Oximeter Readings	Averages Alv.O_2 Press.
1,000	Air	21	95	99
(ground)	Oxygen	12	97	110
3,000	Air	34	94	89
	Oxygen	8	95	90
6,000	Air	33	91	74
	Oxygen	10	93	75
9,000	Air	32	88	61
	Oxygen	8	90	64
12,000	Air	36	83	50
	Oxygen	10	87	54
15,000	Air	33	78	42
	Oxygen	7	80	46
17,000	Air	13	75	39
	Oxygen	2	74	40

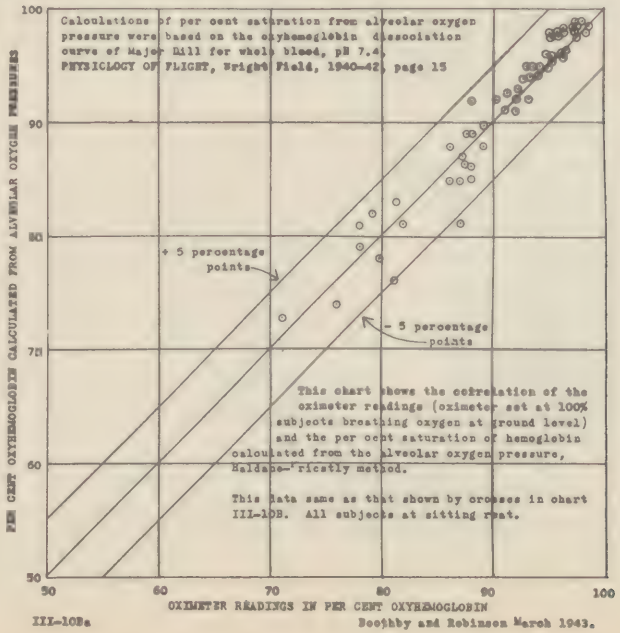
Number of observations = 259.
Observations averaged for each altitude.

Alveolar air, Haldane-Priestly method:
○ = Oximeter set at 95% with subject breathing air at ground level.
X = Oximeter set at 100% with subject breathing oxygen at ground level.

The individual observations comprising the averages are shown in chart III-10B.
All subjects at sitting rest.

The oxyhemoglobin dissociation curves for whole blood are those reported by Major Dill and have been redrawn from PHYSIOLOGY OF FLIGHT, Wright Field, 1940-42, page 15.
III-10A

Boothby and Robinson March, 1943.



Calculations of per cent saturation from alveolar oxygen pressure were based on the oxyhemoglobin dissociation curve of Major Dill for whole blood, pH 7.4. PHYSIOLOGY OF FLIGHT, Wright Field, 1940-42, page 15

This chart shows the correlation of the oximeter readings (oximeter set at 100% subjects breathing oxygen at ground level) and the per cent saturation of hemoglobin calculated from the alveolar oxygen pressure, Haldane-Priestly method.

This data same as that shown by crosses in chart III-10B. All subjects at sitting rest.

III-10Ba

Boothby and Robinson March 1943.

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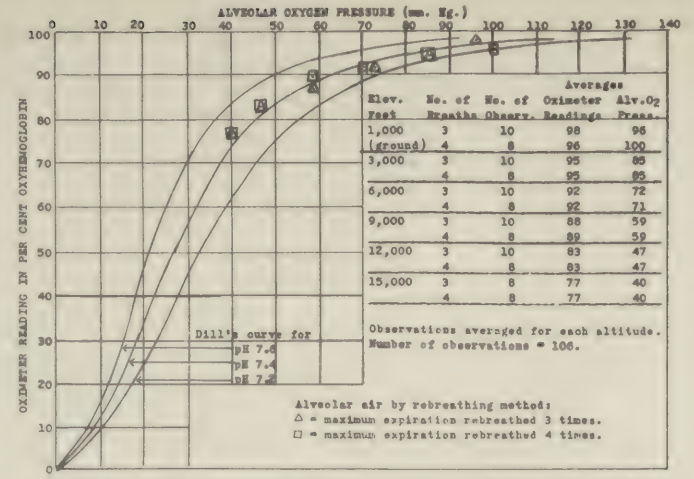
Mayo Aero Medical Unit

COMPARISON OF OXIMETER READINGS AND ALVEOLAR OXYGEN PRESSURES

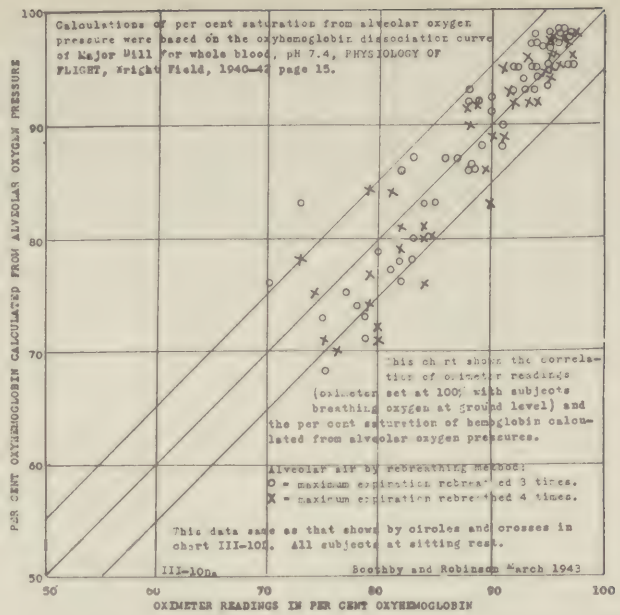


Elev. Feet	No. of Breaths	No. of Observ.	Averages Oximeter Readings	Averages Alv.O_2 Press.
1,000 (ground)	3	10	98	96
	4	8	96	100
3,000	3	10	95	85
	4	8	95	95
6,000	3	10	92	72
	4	8	92	71
9,000	3	10	88	59
	4	8	89	59
12,000	3	10	83	47
	4	8	83	47
15,000	3	8	77	40
	4	8	77	40

Observations averaged for each altitude.
Number of observations = 106.

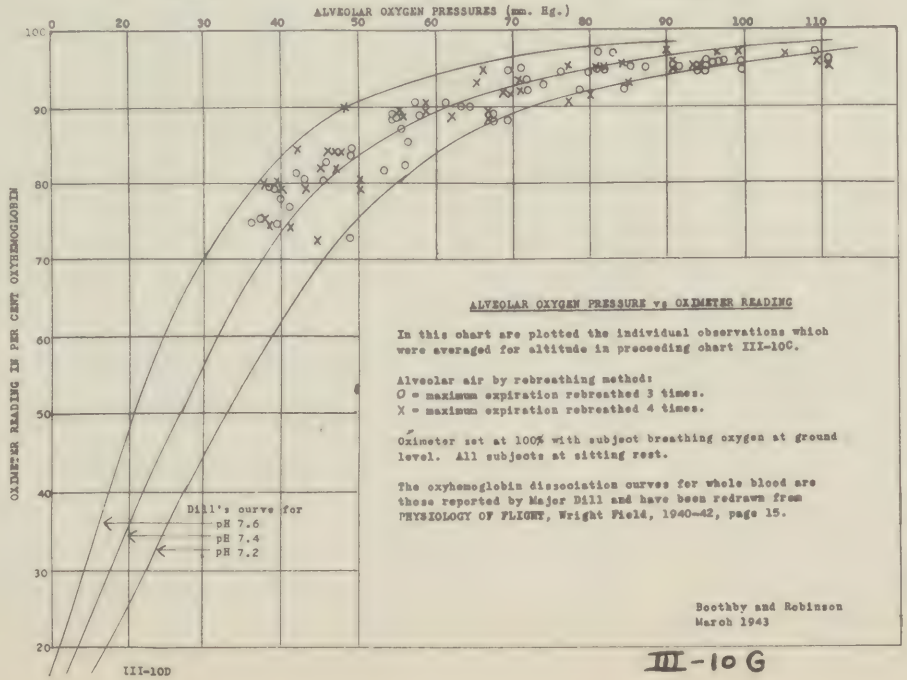
Oximeter set at 100% with subject breathing oxygen at ground level. The individual observations comprising the averages are shown in chart III-10D. All subjects at sitting rest.

The oxyhemoglobin dissociation curves for whole blood are those reported by Major Dill and have been redrawn from PHYSIOLOGY OF FLIGHT, Wright Field, 1940-42, page 15.



III-10C

Boothby and Robinson
March 1943



ALVEOLAR OXYGEN PRESSURE vs OXIMETER READING

In this chart are plotted the individual observations which were averaged for altitude in preceeding chart III-10C.

Alveolar air by rebreathing method:
O = maximum expiration rebreathed 3 times.
X = maximum expiration rebreathed 4 times.

Oximeter set at 100% with subject breathing oxygen at ground level. All subjects at sitting rest.

The oxyhemoglobin dissociation curves for whole blood are those reported by Major Dill and have been redrawn from PHYSIOLOGY OF FLIGHT, Wright Field, 1940-42, page 15.

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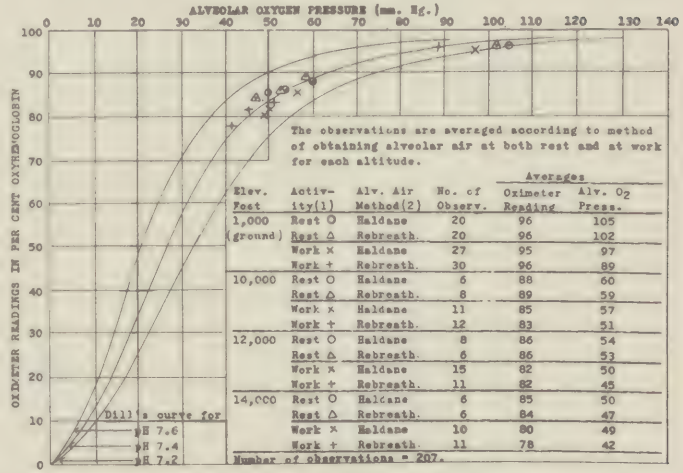
March 1943

III-10D



The observations are averaged according to method of obtaining alveolar air at both rest and at work for each altitude.

Elev. Feet	Activity(1)	Alv. Air Method(2)	No. of Observ.	Averages Oximeter Reading	Averages Alv. O_2 Press.
1,000 (ground)	Rest O	Haldane	20	96	105
	Rest △	Rebreath.	20	96	102
	Work ×	Haldane	27	95	97
	Work +	Rebreath.	30	96	89
10,000	Rest O	Haldane	6	88	60
	Rest △	Rebreath.	8	89	59
	Work ×	Haldane	11	85	57
	Work +	Rebreath.	12	83	51
12,000	Rest O	Haldane	8	86	54
	Rest △	Rebreath.	6	86	53
	Work ×	Haldane	15	82	50
	Work +	Rebreath.	11	82	45
14,000	Rest O	Haldane	6	85	50
	Rest △	Rebreath.	6	84	47
	Work ×	Haldane	10	80	49
	Work +	Rebreath.	11	78	42

Number of observations = 207.

(1) Rest - sitting in chair. Work - stepping onto 5 inch steel 16 times per minute with metronome set at 80 to obtain 5 beats to alternate legs used for elevation.

(2) Alveolar air methods: (a) Haldane-Priestly.
(b) Rebreathing method with single expiration rebreathed 3 times.

Oximeter set at 100% with subject breathing oxygen at ground level.
The oxygen dissociation curves for whole blood are those reported by Major Dill and have been redrawn from PHYSIOLOGY OF FLIGHT, Wright Field, 1940-42, page 15.

III-10E

Boothby and Robinson
March 1943

III-10 G

NATIONAL RESEARCH COUNCIL, DIVISION OF MEDICAL SCIENCES
acting for the
COMMITTEE ON MEDICAL RESEARCH
of the
Office of Scientific Research and Development

COMMITTEE ON AVIATION MEDICINE

Report No. 222
RESTRICTED Date: December 1943

"TRACHEAL" VERSUS "ALVEOLAR" AIR: A REVIEW OF THE METHODS OF SELECTING CERTAIN PHYSIOLOGICAL DATA BEARING ON THE DESIGN OF OXYGEN SUPPLY SYSTEM FOR AVIATORS.

From the MAYO AERO MEDICAL UNIT, Rochester, Minnesota, by Dr. J. B. Bateman; Walter M. Boothby, Responsible Investigator.

Prepared at the request of Dr. Louis B. Flexner, National Research Council.

SUMMARY

1. One point of view favors the tracheal and the other stresses the advantages of the alveolar reference points; the limits and advantages of each are discussed.

2. Attention is drawn to a possible objection to the "alveolar air" equation. It is contended that the role of a relatively stagnant gas layer separating the tidal air from the pulmonary epithelium has never been adequately discussed, although calculations of the composition of alveolar air depend for their validity upon the absence of any such unmixed fraction. For this reason it is unwise to place too much reliance upon theoretical calculations of the alveolar oxygen pressure under different environmental conditions.

3. The alveolar air equation is further examined from the following points of view:

(a) In relation to experimental data on subjects breathing air or pure oxygen at simulated high altitudes, and air-nitrogen mixtures at sea level.

(b) In its bearing on the calculation of specifications for the gas mixtures to be supplied in order to maintain a normal physiological condition in persons at high altitudes. These are compared with the specifications resulting from use of the "tracheal" air standard.

(c) In its application to the calculation of "equivalent altitudes" under conditions involving unavoidable anoxia.

4. The practical suggestion arising from this discussion is that formal adoption of one "reference point" or the other is unnecessary. As a rule it will make little difference which is used; in the case of the anoxic subject, it may make a good deal of difference but recommendations in such cases should be made after due consideration of all available data. The results of theoretical calculations with dubious numerical factors and an equation of questionable validity should not be too widely applied.

5. A simple algebraic nomenclature is proposed for data on the respiratory gases. This has the advantage that it can be typewritten without use of special adjustments or unusual characters.

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PART I. THE COMPOSITION OF ALVEOLAR AIR.

a. The purpose of an oxygen supply system is to prevent or reduce that impairment of human physiological function which would occur if the subject were exposed to the unmodified atmosphere at certain distances from sea level. The final criterion of performance of such a system is therefore its success, when operating with reasonable economy of materials, in enabling persons using it to carry out any necessary tasks and, to a smaller degree, in preventing any detrimental after-effects. Performance tests are, however, so unreliable and subject to such considerable personal variation that this criterion can hardly be used as a basis on which to draw up the specifications of an oxygen supply system. Consequently it is necessary to have recourse to reference points which can be given precise physical definition, with the obvious qualification that apparatus constructed in the light of such secondary criteria must always be subject to any modification suggested by efficiency tests in the field.

Some dispute has arisen concerning the choice of reference point. It is probably agreed that the percentage arterial saturation with oxygen is closely related to efficiency, although the relationship is certainly liable to be obscured by the effects of other physiological variables such as cranial blood flow and by many sources of individual variation including the hyperventilation of anoxia. As a practical reference point this quantity is not to be considered, because of the lack, on the one hand, of sufficiently consistent and extensive experimental data, and on the other hand, of any generally applicable relationship between arterial saturation and the composition of inspired air.

The next reference point which suggests itself is the alveolar oxygen pressure, since this must be directly related to the pressure of dissolved oxygen in equilibrium with arterial blood. There has been some academic dispute between those who advocate the use of this quantity and those who prefer simply to use the partial pressure of oxygen in the inspired gas. The contentions of the former group are based implicitly upon two assumptions:

(1) That in two given environmental situations a subject is in comparable physiological conditions if the alveolar partial pressures of oxygen and carbon dioxide are unchanged.

(2) That there exists a simple algebraical relationship between the respiratory quotient, the composition of inspired air, and the composition of alveolar air, and that this relationship may be legitimately used for the purpose of extrapolation or interpolation to conditions not adequately covered by experimental data. It is furthermore assumed that this equation shows the alveolar oxygen pressure to depend upon other variables in addition to the oxygen pressure in inspired air, making the use of the latter quantity inadmissible as an index of physiologically equivalent states.

The other group, if their position has been properly understood, accept the theoretical validity of the relationship referred to, and therefore do not wish to assert that the partial pressure of oxygen in inspired air is strictly an index of physiological equivalence. They do, however, consider that the use of the alveolar standard and of the theoretical equation connected with it has only the effect of introducing changes which are too small to be detected with certainty in the available experimental data, and which therefore lend to the resulting specifications a misleading and experimentally unwarranted air of precision.

This attitude will be examined in a later section of this paper; the next paragraphs, however, will present a somewhat different point of view. It will be argued that it is at present impossible to derive a useful equation relating the composition of alveolar air - as it will be defined below - to that of inspired air, and that the existing equations are not strictly valid. This argument, if correct, inevitably makes the choice of the inspired oxygen standard the only one that can be defended upon physiological grounds.

b. The metabolic respiratory quotient can be calculated, as is well known, from the composition of the inspired and expired air; an equation exactly similar in form, but containing alveolar partial pressures instead of expired air partial pressure, has been derived in several different ways. These derivations have in common the underlying assumption, explicit or implicit, that the respiratory exchange can be expressed as the conversion of a certain volume of inspired air, by removal of oxygen and addition of carbon dioxide, into a certain new volume of alveolar air. The assumption is implicit in the derivation given by T. Benzinger (Erg. Physiol., 40, 1, 1938) and explicit, notably, in that of J. S. Gray (School of Aviation Medicine, Randolph Field, Texas, Research Report No. 1, 12 April 1943), while F. Brink ("Calculations Relating to the Composition of Alveolar Gas") substitutes alveolar values in his expired air equation without attempting to justify this procedure. Within the limits of correctness of the above assumption, the equation is undoubtedly valid.

Now it would seem probable that a certain fraction of what is collected as alveolar air, together with a residue that is never expelled even in the sharpest expiration, is not thoroughly mixed at each inspiration with fresh tidal air, but may be considered as a stagnant layer which acts as the vehicle, so to speak, of respiratory exchange, without actually itself undergoing periodic changes in composition. This stagnant or partly stagnant layer in intimate contact with the pulmonary epithelium is in a steady state, in which it passes on to the pulmonary capillaries exactly as much oxygen as it receives from the mixture of inspired and alveolar air in contact with it, while transferring to the latter exactly the amount of carbon dioxide that it receives from the blood. Functioning as a buffer in such a way as to reduce the amplitude of fluctuations in the percentage saturation of pulmonary blood, the stagnant layer may be imagined to have the properties common to any system existing in a ture steady state or "dynamic equilibrium." The most significant and familiar of these properties from the point of view of the present discussion is the fact that the composition of the system in the steady state cannot be related in any simple manner to the rate at which matter or energy are passing

through it. Stated explicitly for the present case, it may be said that the partial pressures of oxygen and carbon dioxide in the stagnant layer depend not only upon the rate at which oxygen is being removed and carbon dioxide produced, but also upon the various diffusion coefficients at the two boundaries of the layer. A complete calculation of the composition of the stagnant layer would thus be difficult even for the over-simplified case here visualized; it becomes immeasurably more difficult when we realize that the simple idea of a sharply defined stagnant layer is certainly an abstraction, the real counterpart of which must be highly diffuse. The composition in the region nearest to the pulmonary epithelium will be regulated predominantly by diffusion, while as we move moutward the effects of convection and mechanical mixing will become increasingly important. The effective thickness of the layer, if any single magnitude can be assigned to it under given conditions, will moveover be expected to vary with the depth and rate of breathing in much the same manner as the dead space is known to depend upon these variables.

Restating the thesis algebraically for a sharply defined stagnant layer, we may write the number of molecules of oxygen transferred to the lung during a short time as $\delta\, n(O_2)$ and the corresponding amount of carbon dioxide produced as $\delta\, n(CO_2)$. In terms of the corresponding volumes $\delta\, v(O_2)$ and $\delta\, v(CO_2)$ at the prevailing partial pressures,

$$\delta\, n(O_2) = p(O_2).\,\delta\, v(O_2)/RT \qquad \delta\, n(CO_2) = p(CO_2).\,\delta\, v(CO_2)/RT$$

The metabolic respiratory quotient is

$$R = \delta\, n(CO_2)/\,\delta\, n(O_2) = \frac{p(CO_2).\,\delta\, v(CO_2)}{p(O_2).\,\delta\, v(O_2)}$$

In the steady state the layer will maintain its constant composition by the uptake of $\delta\, n(O_2)$ molecules of oxygen by diffusion from the urrounding alveolar air and loss of $\delta\, n(CO_2)$ molecules of carbon dioxide. Without a knowledge of both the dynamics of these processes and of the magnitude of the respiratory exchanges $\delta\, n$, it is not possible to calculate the composition of the stagnant layer even in terms of that of the rest of the alveolar air.

In view of the fact that the variable which really determines the oxygen tension of the pulmonary blood, and thus to a first approximation the physiological state of the individual, is the partial pressure of oxygen in the stagnant layer, the above conclusion is of some significance. It throws doubt not only upon the validity of calculations purporting to give the composition of alveolar air in terms of that of inspired air; it also implies that even the measured partial pressures of oxygen in alveolar air may not represent quite exactly the steady state values which actually determine the percentage arterial saturation.

If the above arguments, which must be correct in principle, really apply to a significant fraction of the true alveolar air, why has the alveolar gas equation had such apparent success in the interpretation of experimental data? A two-fold answer may be given. In the first place, two circumstances - the relative constancy of alveolar carbon dioxide pressure and the condition that all the constituent partial pressures must add up the prevailing atmospheric pressure - combine to make any possible variations in the partial pressure of oxygen rather small; and a glance at the wide scatter of individual values observed experimentally for the composition of alveolar air will make it clear that from the experimental point of view the decisive testing of the equation involves only second order effects. The most that can be said is that the existing data do not confliot sharply with the requirements

of the equation. Insofar as there appears to be agreement, it may be argued that the collected alveolar samples were not greatly "contaminated" with stagnant layer gas, and do not therefore reflect accurately the value of the physiologically most important quantity. In the second place, it has been observed that respiratory quotients calculated from alveolar analyses are often lower than those found from the total expired air. The explanation given by Haldane, recognizing the importance of diffusion rates in determining the composition of alveolar air, is not fundamentally different from that expressed above, although not carried through to a full statement of its implications: "We have convinced ourselves that the ratio of deficiency of oxygen to excess of CO_2 is higher in the alveolar than in the expired air. The cause of this phenomenon is doubtless the fact that in the smaller bronchioles and so-called 'respiratory bronchioles' the conditions for giving off CO_2 are, on account of its greater solubility, more favorable than for the absorption of oxygen when these parts are filled with pure air at each inspiration." (C. G. Douglas, J. S. Haldane, Y. Henderson and E. C. Schneider, Phil. Trans. R.S., 203B, 185, 1913; cf J. S. Haldane and J. G. Priestley, Respiration, New Haven, 1935, p. 16 ff.).

The importance of the effects here described will not be amenable to final assessment until it becomes feasible to make exploratory measurements of local oxygen and carbon dioxide pressures in different parts of the respiratory passages.

PART II. ALVEOLAR VERSUS INSPIRED OXYGEN PRESSURE AS A PRACTICAL REFERENCE POINT FOR THE CALCULATION OF EQUIVALENT ALTITUDES WHILE BREATHING GASES OTHER THAN AIR.

It is improbable that any decision will be reached immediately concerning the justice of the above arguments, which attack the premiss rather than the manner of application of the alveolar air equation. We wish now to ignore these criticisms and to examine the arguments for the inspired air and alveolar air reference points solely on the basis of the opposing points of view expressed on page 2. It will be necessary to show how much difference there is between specifications based upon the two standards, and to find whether these differences have any practical significance that can be demonstrated unequivocally by existing experimental data.

A simplified nomenclature may be appropriately introduced at this point. We shall consider that air breathed changes in composition in five stages indicated by the number of dashes:

dry inspired air	'
moist inspired ("tracheal") air	"
moist alveolar air	"'
moist expired air	""
dry expired air	""'

Partial pressure of a component will always be p ; fraction of a component, f ; total or barometric pressure, P ; respiratory quotient, Q ; oxygen, O ; carbon dioxide, C ; nitrogen, N . The partial pressure of saturated water vapor at body temperature will be given always as the numerical value 47. Thus:

f' (O) = fraction of oxygen in dry inspired air.
p" (O) = partial pressure of oxygen in moist inspired air.
p"'(C) = partial pressure of carbon dioxide in moist alveolar air.

The alveolar air equation may be written as follows:

$$p''(0) = p''(0) - p''(C)/Q + f'(0).p''(C).(1-Q)/Q \qquad (1)$$

whenever it may be assumed that p'(C) is zero.

With the equation in this form it is immediately apparent that the alveolar oxygen pressure is given by two terms. The first involves the inspired or "tracheal" oxygn pressure as such; the second involves the fraction of oxygen in the inspired air or, in other words, the fraction of nitrogen. Under certain circumstances the second term is zero: namely, if Q is unity, or (to take a case which cannot be realized in practice) if f'(0) is zero and pure nitrogen is being inhaled. In this case, provided the alveolar carbon dioxide pressure is constant, the partial pressure of oxygen in the alveoli is strictly proportional to that in the inspired air, and the inspired air standard is just as accurate as the alveolar air standard. Under all other circumstances the presence of the second term makes it clear that it is by no means "a matter of indifference whether oxygen lack is induced by decreased pressure or by breathing nitrog Assuming an alveolar carbon dioxide pressure or 40 mm. Hg and a respiratory quotient of 0.8, the reduction of oxygen pressure in the alveoli produced by metabolic exchange would be 40 mm. Hg if pure oxygen were breathed, and 50 mm. Hg in the limiting case of inhalation of pure nitrogen." (T. Benzinger, loc. cit., p.41). Whether this extreme difference of 10 mm. Hg in the alveolar oxygen pressure which results from removal of nitrogen has been demonstrated in practice can only be decided by an appeal to experimental data. The most extensive are those obtained by Boothby and his colleagues for subjects breathing pure oxygen at 35,000, 40,000 and 42,000 feet, and the alveolar pressures thus determined may be compared with those found in subjects breathing air at altitudes corresponding to the same inspired oxygen pressures as those prevailing during the breathing of pure oxygen. The sensitiveness of the comparison is somewhat reduced by the presence of nitrogen of unknown origin in the alveolar samples when pure oxygen was being inhaled; this represents, however, an uncertainty that is probably inevitable with present mentods. In the data as here quoted, the inspired oxygen pressures have been calculated both with and without correction for the contaminating nitrogen, which has been assumed in the one case to have originated in a leak of air during inspiration and in the other in some unspecified manner, such as nitrogen elimination from the body.

In Table 1, which is explained more fully in the legend, columns (4) and (8) represent directly comparable values of the alveolar oxygen pressure, at equal "tracheal" oxygen pressures, with and without the presence of nitrogen. It is evident that although the uncertainty in the values of p"(0) tends to obscure the effect, there is nevertheless a distinct difference in the sense predicted by the formula, but somewhat smaller in magnitude.

At the other end of the scale, where the effect of altitude is produced by adding nitrogen to the inspired air, the decrease in alveolar oxygen due to added nitrogen should be smaller than in the case already considered. This is obvious from equation (1), since the effect produced is proportional to f'(0), and the range of values from air to pure nitrogen is only one quarter of the range from air to pure oxygen. This is in agreement with the fact that Boothby's mean curve for the change of p"(0) for subjects breathing air at decreased pressure was found also to fit the corresponding set of values for subjects breathing air-nitrogen mixtures at ground level (1,000 ft.)

Turning now to the practical implications of Table 1, we see that if a regulator is so designed as to provide a gas mixture with a partial pressure of oxygen which remains constant as the altitude is increased, a certain amount of unnecessary

waste is incurred by reason of the fact that when the regulator is providing oxygen at such a rate, for example, as to give an inhaled mixture containing about 50 per cent oxygen, the alveolar oxygen pressure may be raised about 2.6 mm. Hg above its value when air is breathed; if 75 per cent oxygen is inhaled, the increase would be 4.9 mm., and 7.1 mm. for pure oxygen. Thus it would seem reasonable to permit a certain gradual linear decrease of oxygen pressure in the inspired gas during the transition from air to pure oxygen.

Exactly how much economy could be achieved in this way can best be seen by a calculation of the kind represented by Brink's chart A3. Rearranging equation (1) and substituting

$$p''(O) = f'(O).(P - 47) \qquad (2)$$

we find

$$f'(O) = \frac{p''(O) + p'''(C)/Q}{(P - p'''(C) - 47) + p'''(C)/Q} \qquad (3)$$

which enables us to calculate the fraction of oxygen in air which at any altitude P will correspond to a given value of the alveolar oxygen $p''(O)$. If the inspired gas is prepared by mixing air with a fraction $F'(O)$ of pure oxygen, then

$$F'(O) = 1.26\, f'(O) - 0.264 \qquad (4)$$

On the constant "tracheal" oxygen criterion, on the other hand, the values of $f'(O)$ can be obtained from equation(2).

The discrepancy between results based on the two criteria being greatest when pure oxygen is being breathed, it suffices to compare values of $f'(O)$ or $F'(O)$ calculated for a value of P at which a very high proportion of oxygen is needed in order to keep the alveolar, or the "tracheal" oxygen pressures, as the case may be, at sea level values. Let P = 200 mm. A convenient value for $p'(O)$ is 100 mm. In Table 2 figures for $f'(O)$ and $F'(O)$, calculated from equation (3), are given for the following cases:

$p'''(C) = 36 \qquad Q = 0.82$
$p'''(C) = 45 \qquad Q = 0.82$
$p'''(C) = 36 \qquad Q = 1.00$

These are compared with the values obtained from equation (2) for the case

$$p''(O) = 142 \text{ mm.}$$

The greatest possible saving of oxygen as a result of using the alveolar reference point is represented by a difference of 0.905 - 0.862, or 0.043, or about 5 per cent, in the amounts of oxygen needed. Probable physiological variations among personnel tend to reduce this difference, so that it may be doubted whether anything is gained in this case by insisting on the alveolar criterion. The same argument holds if it be agreed to save oxygen by supplying only enough gas to maintain the subject at, say, a 10,000 foot level.

At altitudes where the sea level values cannot be maintained even by breathing pure oxygen, it is desirable to be able to estimate the probable effects of a given altitude by reference to the physiologically equivalent altitude when air is being breathed. Similar data are also desirable for the effect of breathing various mixtures of air and oxygen at high altitudes. In constructing charts of equivalent altitudes, it is of course possible again to use either the "tracheal" or the alveolar air reference point. Here, however, the matter is often complicated by the effects of anoxia, and in applying the alveolar air formula there arises the

question of choice of appropriate values for Q. This will be illustrated here by some calculations for air and pure oxygen. All quantities referring to air breathing will be denoted by an asterisk and the formulas are the same as used by Brink for the same purpose.

Combining equations (1) and (2) we may write for a subject breathing air:

$$p"'(O)^* = 0.209\ (P^* - 47) - p"'(C)^*/Q + 0.209\ p"'(C)^*\ (1-Q)/Q \qquad (5)$$

and for subject breathing oxygen:

$$p"'(O) = P - 47 - p"'(C) \qquad (6)$$

For equivalent altitudes

$$p"'(O)^* = p"'(O)$$

$$p"'(C)^* = p"'(C) \qquad (7)$$

Combining (5) and (6) and retaining the symbol $p"'(C)^*$, for which there are experimental values, we get

$$P = 0.209\ (P^* - 47) - 0.791\ p"'(C)^*\ (1-Q)/Q + 47 \qquad (8)$$

In applying equation (8), Brink used values of $p"'(C)^*$ taken from Boothby's data, together with the probable "true" or steady state respiratory quotient Q, 0.82. In this way he obtained equivalent altitudes for a hypothetical steady state which in many cases can never be attained because of the accumulating effects of anoxia. To this extent his results are dubious, and it might be considered preferable to use in equation (8) those non-stationary values of Q which are in fact essential to the mutual consistency of the experimental data and equation (1). It is true that results obtained in this way should be treated with reserve, but this is no reason for retreating to an entirely artificial position. Lutz and Schneider (B. R. Lutz and E. C. Schneider, Am. J. Physiol.; 50, 280, 1919), to be sure, succeeded in establishing the stationary values of Q after a 40 minute stay at 18,000 feet, but at this and still more at higher altitudes, the important information from a practical point of view would seem to be that defining the condition of the subject as it is established temporarily by the expedient of hyperventilation. Interesting remarks on this question are given in the paper of J. S. Gray (loc-cit).

In Table 3 we give, for what they may be worth, values of the equivalent altitude calculated in three ways:

(1) Brink's method, using Boothby's $p"'(C)^*$ values and Q = 0.82. Numerical values as follows (altitudes are in thousands of feet):

Altitude	0	5	10	12	14	16	18	20	22	24
P	760.0	632.3	522.6	483.3	446.4	411.8	379.4	349.1	320.8	294.4
$p"'(C)^*$	40	38	35.5	35	34	33	32	30	28	25

(2) Applying equation (8) to experimental values of Q, the apparent respiratory quotient in a non-stationary state. Numerical values as follows calculated from Boothby's smoothed curves for $p"'(O)^*$ and $P"'(C)^*$.

P	700	650	600	550	500	450	400	350	300
p"'(0)*	94.2	83.5	73.3	63.6	54.6	46.2	39.2	34.0	30.5
p"'(C)*	36.7	36.6	36.2	35.8	35.2	34.2	32.6	30.0	26.0
Q	0.839	0.830	0.825	0.832	0.851	0.876	0.929	1.029	1.214

(3) Equal inspired oxygen pressures:

$$P = 0.209\ (P_{*}-47)/f'(0) + 47$$

To these are added:

(4) Experimental equivalents for air-breathing and oxygen-breathing, taken from Boothby's data on a basis of equal observed alveolar oxygen pressures.

It will be observed from Table 3 and from Fig. 1, where the data are plotted, that the equal inspired oxygen figures provide a somewhat more cautious estimate of the equivalent altitudes than do Brink's data. This is merely the result of the nitrogen effect already discussed. It amounts to a possible overestimate of the equivalent altitudes by about 1,000 feet at 33,000 feet, increasing to nearly 2,000 feet at 45,000 feet. On the other hand, the calculation using non-stationary-state values of Q leads to a curve which approaches and even crosses the inspired oxygen curve in the region of anoxia. The experimental figures tend to follow the equal alveolar oxygen curves, but they are subject to the same uncertainty as that pointed out in Table 1.

The suggestion seems warranted that charts of equivalent altitudes should follow curves (1) and (2) in the lower altitude range and should at higher altitudes deviate increasingly from (1) in the sense indicated by curve (2), with perhaps an increased thickness of the line to indicate the added possibilities of error in any data given for anoxic subjects (Fig. 2). Such a curve for 100 per cent oxygen will be nearly identical with that given by Gray (l.c.).

It is scarcely possible to pursue this discussion further without detailed knowledge of the amount of practical importance which attaches to accurate statement of equivalent altitudes. It is clear that present knowledge is sufficient for the construction of oxygen supply and equivalent altitude charts which do not dangerously distort the physiological picture. Certain ill-controlled variables, notably leakage of air into the inspired gas, have been disregarded, and must be taken into account before the specifications are finally turned over to the engineers. We are not competent to express any opinion on this point.

Concerning the argument over reference points, we contend that the foregoing discussion shows it to have been largely superfluous. We are not scholastics, committed irrevocably to one view or the other. Our business is only to provide specifications for engineers who are quite unconcerned about the manner in which they were drawn up. If it is convenient at one point to work on the basis of inspired air and at another to make calculations involving alveolar air, this double procedure should be judged solely by the practical effectiveness of the resulting statement of physiological requirements.

Table 1.

Breathing Oxygen				Breathing Air				Effect of Nitrogen	
								Found	Predicted
(1) p"(0)	(2) Mean p"(0)	(3) h	(4) p"'(0)	(5) p"(0)	(6) h	(7) p"'(0) extremes	(8) p"'(0) corresponding to mean in Col. (1)	(9)	(10)
131.7 125.7	128.7	35,000	88.7	131.7 125.7	3208 4373	88.7 82.8	85.7 85.7	3.0	7.1
93.8 90.0	91.9	40,000	56.0	93.8 90.0	11394 12341	53.6 50.5	52.1	4.9	7.1
80.9 77.0	79.0	42,000	45.7	80.9 77.0	14740 15806	43.7 41.0	42.3	3.4	7.1

The data for breathing oxygen give experimental average values of alveolar oxygen pressures at the specified altitudes. The "tracheal" oxygen pressures in the first column are presented in pairs which represent the uncertainty caused by the presence of measurable amounts of nitrogen in the alveolar air.

In obtaining the figures for subjects breathing air use was made of the smoothed curves of alveolar oxygen pressures given in Boothby's charts of 1313 observations. The values of p"'(0) read from this curve correspond to the same p"(0) values that prevailed in the experiments breathing oxygen.

Table 2.

P = 200 mm. Hg throughout.

Altitude = 32,610 feet

	p"'(C)	Q	f'(O)	F'(O)
Constant alveolar oxygen, p"'(O) = 100 mm.	36	0.82	0.894	0.862
	45	0.82	0.957	0.942
	36	1.00	0.882	0.882
Constant inspired and "tracheal" oxygen, p"(O) = 142 mm.	-	-	0.928	0.905

Table 3.

Equivalent Altitude, breathing air		Equal Alveolar Oxygen Pressures (1) Stationary State		(2) Non-stationary State		Equal Inspired Oxygen Pressures (3)		Experimental Values (4)	
h*	P*	h	p	h	p	h	P	h	P
0	760.0	33.8	189.1	33.7	190.1	33.0	196.0	-	-
3.25	674.8	35.8	172.0	35.7	172.8	35.0	178.7	35.0 35.7	
10.7	508.6	40.4	138.1	40.6	136.8	39.6	143.5	40.0 40.6	
14.0	446.4	42.6	124.6	42.2	126.7	41.6	130.5	42.0 42.7	
18.0	379.4	45.0	110.9	44.2	115.2	44.0	116.5	-	-
20.0	349.1	46.2	104.9	45.1	110.3	45.1	110.1	-	-
22.0	320.8	47.3	99.4	45.8	106.7	46.3	104.2	-	-
24.0	294.4	48.4	94.4	46.3	104.2	47.4	98.7	-	-

LEGEND TO FIGURE I.

Effective or equivalent altitudes (ordinate) of subjects breathing pure oxygen at various actual altitudes (abscissa).

Curve 1: calculated on a basis of equal partial pressures of oxygen in the inspired or "tracheal" air.

Curve 2: calculated from the alveolar air equation (in the form of equation 8), using experimental values of the alveolar carbon dioxide pressure and an assumed "steady state" respiratory quotient, Q, of 0.82.

Curve 3: calculated from the alveolar air equation (equation 8), using experimental values of the alveolar carbon dioxide pressure and the apparent or "non-stationary" values of the respiratory quotient calculated from Boothby's data using equation 1.

LEGEND TO FIGURE 2.

Equivalent altitude chart suggested by the curves given in Figure 1 (see text).

FIGURE 1

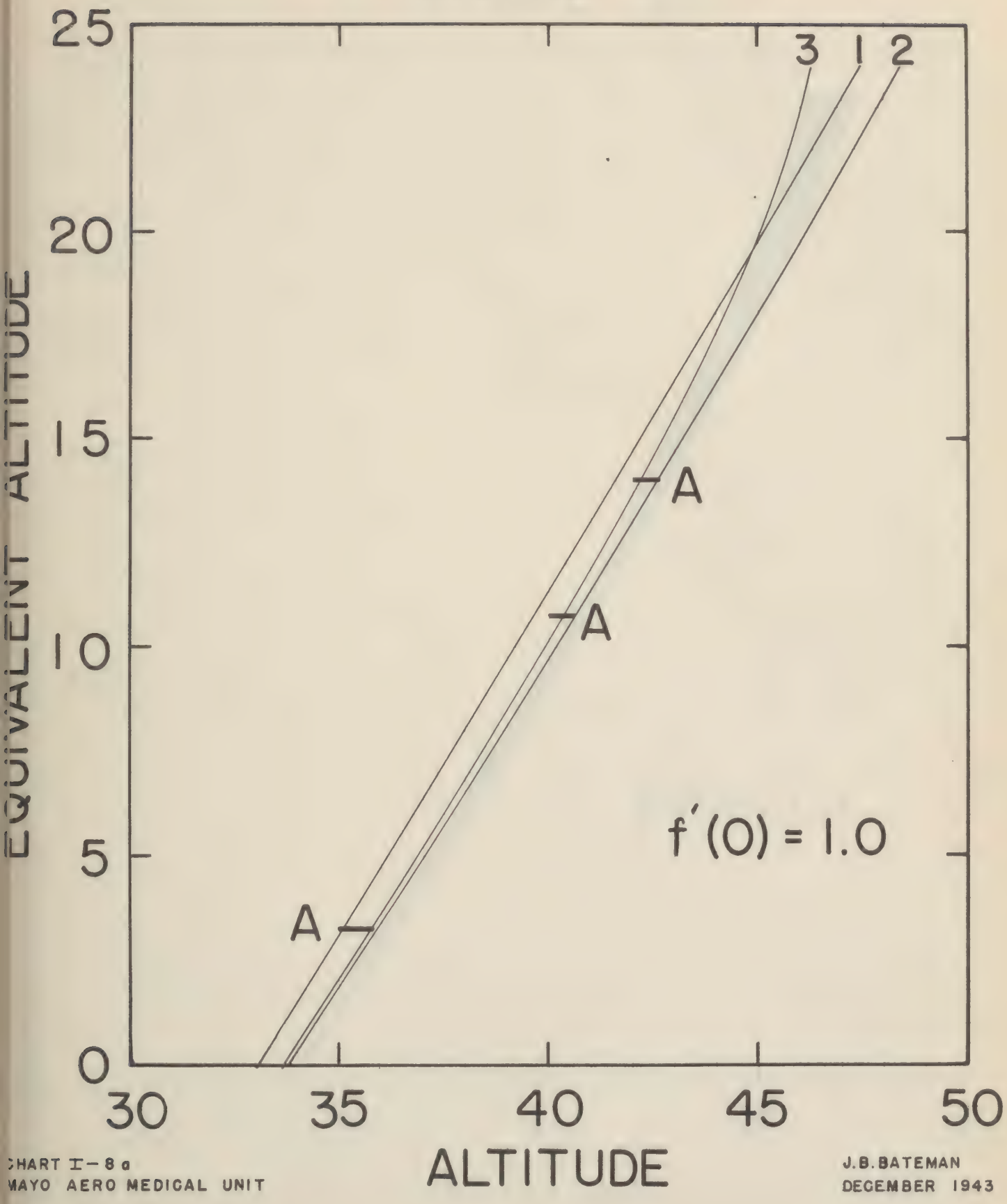

CHART I–8 a
MAYO AERO MEDICAL UNIT

J.B. BATEMAN
DECEMBER 1943

FIGURE 2

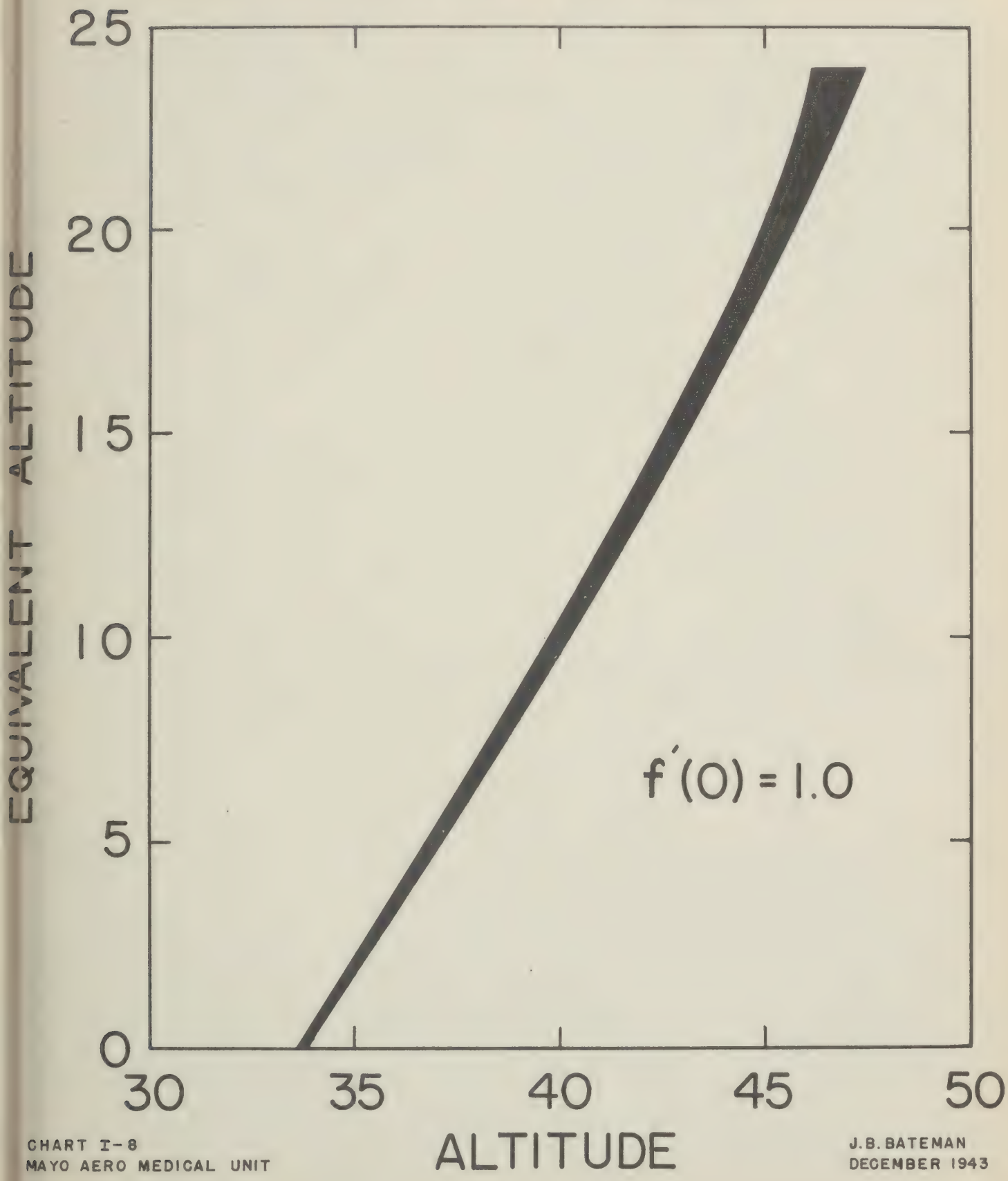

CHART I-8
MAYO AERO MEDICAL UNIT

J.B. BATEMAN
DECEMBER 1943

NATIONAL RESEARCH COUNCIL, DIVISION OF MEDICAL SCIENCES

acting for the

COMMITTEE ON MEDICAL RESEARCH
of the
Office of Scientific Research and Development

COMMITTEE ON AVIATION MEDICINE

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OXYGEN AND AIR PRESSURE AT VARIOUS ALTITUDES AS THEY INFLUENCE THE EFFICIENT FUNCTIONING OF THE AVIATOR.*

By Walter M. Boothby, from the Mayo Aero Medical Unit, Rochester, Minnesota.

Note: This paper was written and submitted in its present form to the Committee on Medical Research, Office of Scientific Research and Development, for publication as a C.M.R. report on August 28, 1942. Through oversight the paper became "lost" and is being issued now, October 1944, but as of the original date and without change although subsequent studies by Wildhack, Brink, Gray, Bateman, Fenn and others have perfected the "alveolar air formula" and elucidated its applicability as well as its limitations. The "tracheal air formulation," however, remains the point of reference for calculating specifications for designing oxygen equipment for aviation.

ABSTRACT

Change of altitude will affect oxygen and air pressure in relation to body needs through various factors, some physical and some physiologic. In the following sections an attempt has been made to trace separately the effect of these factors one at a time successively. In fact, however, they will act simultaneously to produce a very predictable end result. This is especially true as will be seen in the examples given in Part II in which we trace the effect on the atmospheric air of known composition as it is inhaled and comes into final equilibrium in the pulmonary alveoli with the gases of the arterial blood. In Part I the presentation will be limited mainly to the effect of water vapor.

This analysis has been carried out in considerable detail to help those investigators, many of them engineers new to the subject, who now find themselves assisting in the development, testing or comparing, of the various types of oxygen equipment to be used by aviators.

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* We are indebted to Major Joseph Berkson, (MC) of the Air Surgeon's Office for assistance in the elucidation of this problem. Before going on active duty Major Berkson helped in the calculations and in the construction of the charts so that the physiological factors and physical factors involved could be presented diagrammatically as an aid to engineers. The calculations have also been checked by E. J. Baldes, Ph.D.

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MAYO AERO MEDICAL UNIT

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OXYGEN AND AIR PRESSURE AT VARIOUS ALTITUDES AS THEY INFLUENCE THE EFFICIENT FUNCTIONING OF THE AVIATOR*

"Tracheal" air [(B-47) fO_2]

Walter M. Boothby, M. D., Chairman

Part I. Effect of Water Vapor

Change of altitude will affect oxygen and air pressure in relation to body needs through various factors, some physical and some physiologic. In the following sections an attempt has been made to trace separately the effect of these factors one at a time successively. In fact, however, they will act simultaneously to produce a very predictable end result. This is especially true as will be seen in the example given in Part II in which we trace the effect on the atmospheric air of known composition as it is inhaled and comes into final equilibrium in the pulmonary alveoli with the gases of the arterial blood. In Part I the presentation will be limited mainly to the effect of water vapor.

This analysis has been carried out in considerable detail to help those investigators, many of them engineers new to the subject, who now find themselves assisting in the development, testing or comparing, of the various types of oxygen equipment to be used by aviators.

1. Effect of altitude on total atmospheric pressure.

Basically the atmospheric pressure is the weight, per unit area, of the column of air above the position at which the pressure is measured. Therefore, if the density of the air were constant, the pressure would decrease uniformly with increase of altitude. But, because of a number of factors, the density is not constant. The weight of the air exerts a pressure on the air below it and the density at any point therefore depends on the pressure. Mathematically it would follow from this effect alone that the decrease of pressure with increase of altitude would be logarithmic. But there are other factors, chief among them being that the temperature is lower at the higher altitudes, owing in part to the cooling of air when it expands as it rises to a position of lower pressure. The cooling at higher altitudes in turn has the effect of increasing the density and accordingly increasing the pressure at any point below. An equation has been set up for the altitude in terms of the measured air temperature and the air pressures. The decrease of temperature with increase of altitude on the average is fairly uniform (2° C. per 1,000 feet),

* We are indebted to Major Joseph Berkson, (MC) of the Air Surgeon's Office for assistance in the elucidation of this problem. Before going on active duty Major Berkson helped in the calculations and in the construction of the charts so that the physiological factors and physical factors involved could be presented diagrammatically as an aid to engineers. The calculations have also been checked by E. J. Baldes, Ph.D.

and is used to set up an empirical linear equation of the temperature at various altitude By combining this equation of the cooling effect and the basic logarithmic relation a standard atmosphere for reference is defined in which the pressure at any altitude can be computed. At atmosphere assumed to be at 15° C. and a pressure of 760 mm. (mercury barometer) at sea level and containing no moisture has been accepted as the U. S. Standard Atmosphere for aeronautic purposes. For this standard atmosphere the pressure at various altitudes has been calculated and tabled.* This data is charted in curve 1 of figure 1, In this country actual altitude accords fairly well with the atmospheric pressure values so calculated except for extreme seasonal changes which are not to be considered here.

2. Oxygen pressure in the air of the atmosphere.

The atmospheric air is composed largely of oxygen (20.93 per cent) and nitrogen (79.04 per cent) with a small amount of carbon dioxide (0.03 per cent). It also contains minute quantities of other rare gases which are, like nitrogen, inert and can therefore, for present purposes be treated as a part of the nitrogen fraction. The percentage of all these gases is very closely constant at all altitudes so far studied. Measured relatively in terms of the volume that would be occupied by each gas, the fractions of oxygen and nitrogen in dry air are close to ~~0.2903~~ 0.2093 (20.93 per cent) and 0.7904 (79.04 per cent) respectively, and the fraction of carbon dioxide is 0.0003 (0.03 per cent) in the mixture of gases. The pressure exerted by each constituent gas is proportional to its percentage volume. Thus, if the total pressure of atmospheric air is B, the partial pressure of oxygen is 0.2093 x B and the partial pressure of oxygen in the dry atmospheric air is 20.93 per cent of the total atmospheric pressure of dry air at that elevation.

The volumetric fraction of oxygen in dry atmospheric air usually used by physiologists is either 20.93 per cent or 20.94 per cent although the latest values given by Humphreys quoting from Hann and Süring and from Paneth is 20.95 per cent (W. J. Humphreys. Physics of the Air, McGraw-Hill Book Co., Inc., New York and London. 1940, P. 68 and 81). For most practical purposes the value for oxygen can be rounded off to 21 per cent.

Physiologists always use the percent of oxygen in dry air as the basis of their calculation because a definite allowance for the pressure of water vapor in the lungs and body cavities must always be made. This allowance is very easy to compute as will be described later as it always corresponds to the body temperature with which the gas is in equilibrium; this body temperature is usually assumed to be 37° C. and at this temperature the pressure of water vapor in saturated air is 47 mm. It is possible that the vapor pressure of body fluids, especially on curved surfaces, departs somewhat from that of pure distilled water. Also the temperature will vary considerably under different conditions. However, for physiologic purposes the value of 47 mm. has been accepted as a fair average value.

The value for oxygen of 20.75 per cent frequently used by aeronautical engineers is a percentage value based upon air assumed to contain an average amount of water vapor at 15° C; Humphrey, quoting from Hann and Süring, states that this average value for oxygen will vary depending on the amount of moisture present, from 20.44 per cent at the equator to 20.94 per cent at 70° N.

* National Advisory Committee for Aeronautics, Report No. 538; Altitude-Pressure Tables, W. B. Brombacher, 1935.

In the next Section (3) the method of making allowances for water vapor is described in detail when the volumetric fractions of dry atmospheric air are taken as 20.93 per cent for oxygen, 79.04 per cent for nitrogen (including other inert rare gases) and 0.03 per cent for carbon dioxide. The above values are used here because they are those obtained by carefully calibrated volumetric gas analyzers like the Haldane which gives the results in the terms of the dry gases; however, a small amount of liquid water must be present so that the gas being analyzed is completely saturated with water vapor at all burst readings in order to give an accurate per cent on the basis of dry air by the cancellation out of the water vapor when the volume contracts as the result of the absorption of the ideal gases.

Curve II of figure 1 gives the partial pressure of oxygen in the atmosphere calculated as 0.2093 times the values given by curve I which is the total standard atmospheric pressure for various altitudes. In figures 1, 2 and 3 the altitude is scaled on the abscissa in feet because we are interested there in the physical factor of atmospheric pressure in relation to altitude.

In other places where we are interested in graphic representations of physiologic figures as in figure 4, the altitude will be given in its equivalent pressure because the physiologic factors are related to pressure expressed directly and not to elevation as such, as the latter is a modified logarithmic function of density.

3. Effect of saturation of air or gas mixture with water vapor.

In Sections 1 and 2 we have considered the air as though it were dry, that is, free of water vapor. As a matter of fact, owing to the ubiquitous presence of water, the atmospheric air contains water vapor in various amounts. Water vapor evaporates from liquid water into the atmosphere surrounding it until the pressure of the vapor reaches a certain value, determined by its temperature, at which point the atmosphere is said to be saturated. At 37° C., the average temperature of the body, the pressure of water vapor in a saturated atmosphere is 47 mm. The presence of water vapor in the air will therefore change the partial pressures of the ideal gases in the air, namely, oxygen and nitrogen (the latter including the rare gases).

The atmosphere gases, oxygen, nitrogen and carbon dioxide within negligible limits are "ideal" or "true" gases and follow very closely the three gas laws.

(1) Boyle's Law: at any stated temperature a given mass of gas varies in volume inversely as the pressure. (2) Charles' Law: the volume of a gas at a constant pressure varies directly with the absolute temperature. (3) Avogadro's Law: equal volumes of gases with the same temperature and pressure contain an equal number of molecules.

Water vapor is not considered as a "true" or "actual" gas because under the temperature conditions being discussed it does not follow the three laws of ideal or true gases. The pressure of saturated water vapor in the presence of liquid water is dependent only on temperature and, unlike true gases at this temperature, entirely independent of the size of the available space. Water vapor is not compressible with increase in pressure as the size of the space in which it is present is decreased as happens with true gases. Water vapor as such no longer exists as the size of the space decreases because it condenses back into liquid water which relatively speaking occupies no space.

Example 1. Consider a liter of dry air at 37° C. and suppose there to be a diaphragm on the top of it that is freely movable with expansion of the air. Introduce some water at 37° C. Water vapor will arise from the liquid water into the space occupied by the gases, exert an additional pressure on the diaphragm, and the total volume will increase as illustrated on the right-hand side of figure 2. As the volume increases, the pressure exerted by nitrogen and oxygen which together in the first place exerted a pressure equal to the atmospheric pressure, will decrease according to Boyle's law, that is, the partial pressure of these two gases will decrease in inverse proportion to the increased volume. The expansion of the gases will continue until the total pressure exerted by the water vapor and the nitrogen and oxygen together will be equal to the atmospheric pressure B. That is, when equilibrium is reached the pressure of water vapor (47 mm. at 37° C.) plus the pressure exerted by the oxygen and nitrogen will be equal to the atmospheric pressure. Therefore, at equilibrium the pressure of oxygen and nitrogen together but without the water vapor will have decreased by 47 mm. Since according to Boyle's law the volume will be inversely proportional to the pressure, the volume occupied by the oxygen and nitrogen after saturation will be to the volume before saturation as B is to (B -47). The effect of saturating dry air at 37° C. and at atmospheric pressure B, therefore, is to increase the volume in the proportion B/(B - 47) and to decrease the partial pressure of each constituent gas in the proportion (B - 47)/B.

Curve III of figure 2 gives for various altitudes the value of this proportionality factor by which the partial pressure of all the gases or of each constituent gas in dry atmospheric air at 37° C. is decreased when the previously dry air, after contact with liquid water, becomes saturated with water vapor.

According to what has been outlined, if in figure 2 we multiply the partial pressure of oxygen in the atmospheric air dry given in Curve II by the factors given in Curve III, we obtain the partial pressure of oxygen in the atmospheric air saturated with water vapor at 37° C. as shown in Curve IV. It is convenient to remember that this factor makes the oxygen pressure in Curve IV of atmospheric air saturated at 37° C. with water vapor 10 mm. less (9.8 mm. to be more exact) than the corresponding value of Curve II which represents the oxygen pressure in dry atmospheric air. Inspired air before gaseous exchange takes place but after it has reached the body temperature of 37° C. and become completely saturated with water vapor as it passes through the warm moist nasal, tracheal and bronchial passages, may be conveniently designated by the arbitrary term "tracheal air."

Another common way of obtaining the water vapor correction for the pressure of oxygen in tracheal air (air saturated with water vapor at 37° C.) is as follows:

$$PT_{O2} = (B - 47)\ 0.209$$

Where PT_{O2} = pressure of oxygen in tracheal air.

A point which at first sight is confusing is that the varying amount of water vapor or humidity present in the atmospheric air before inhalation can be omitted from the calculation; this can be done because under ordinary conditions the temperature and therefore the water vapor is less than that in the alveolar air. The reason in more detail is that the body is always dealing with the air in the lungs or other body cavities completely saturated with water vapor at 37° C. (body temperature); it makes no difference, therefore, whether the air before entering the body is completely dry, partially saturated or completely saturated as long as the temperature of the

gas is below or equal to body temperature. The final partial pressure of water vapor in the body with which the blood is in essential equilibrium is 47 mm.* which is that corresponding to the average body temperature of 37° C.

As mentioned before, volumetric methods of gas analysis like the Haldane and other similar methods express the percentage of carbon dioxide, oxygen and nitrogen in terms of dry air because the water vapor in each fraction of gas absorbed by the reagent is condensed out although the proportionality is the same if both be considered saturated at the same temperature. The easiest way to allow for water vapor in most physiological problems is to consider the proportion of true gases present in a mixture, the volume of which has been reduced to the dry basis, and to allow for the presence of water vapor by deducting the partial pressure of the water vapor from the barometric or total pressure of the gases with the water vapor present. However, whenever measuring the volume of gases, care must be taken to make the physical conditions such that at least a small amount of liquid water is present in the container holding the gases which are being measured so that the entire gas mixture is completely saturated with water vapor. The temperature at which the gases are measured as well as the barometric pressure must be accurately known, otherwise considerable error may be caused. Comparison of gas volume must always be made at the same temperature and barometric pressure either absolutely dry or completely saturated.

Example 2. Consider a liter of dry air at 37° C. in a confined space with an immovable diaphragm corresponding to a closed body cavity instead of a movable diaphragm corresponding to the alveolar spaces just discussed. Introduce some water at 37° C. Water vapor will arise from liquid water into the space occupied by the gases and exert an additional pressure on the diaphragm inside equal to 47 mm., the vapor pressure of water. The volume has been unable to increase, therefore, the total pressure (P_t) has increased 47 mm. and therefore: $B + 47 = P_t$. Obviously the partial pressure of oxygen and of nitrogen is unchanged because these gases on the dry basis occupy the same volume as before and therefore their respective partial pressures are unchanged. $P_{O_2} = .209 \left[(B + 47) - 47\right] = .209 (P_t - 47) = .209\ B$

Although the oxygen partial pressure (and similarly the nitrogen) in this instance was unchanged, the total pressure was changed by the introduction of water into dry air in a confined space. At 37° C. this resulted in an increased pressure in the ratio of $\frac{P_t}{B}$ which is the same as $\frac{B + 47}{B}$. Now if we remove the extra pressure of 47 on the diaphragm and allow the gases to expand until equilibrium with B is reached to occupy an enlarged volume in the proportion $B/(B - 47)$, then our example in the previous section returns and $P_{O_2} = .209\ (B - 47)$ because now the same amount of oxygen occupies a greater space and therefore the partial pressure of the oxygen is correspondingly decreased.

Example 3. Consider a closed gas cavity like the stomach, intestines or pneumothorax and assume for simplicity that this cavity is freely expansible (like the diaphragm in the first example). At body temperature of 37° C. any air in this cavity will be saturated with water vapor because the walls of the cavity are moist with body fluids. Therefore, the pressure of the gases, P_G, nitrogen, oxygen and

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* Note - The value 47 mm. is generally accepted by physiologists as representing the vapor pressure of tissue and body fluids. Under certain conditions the true value may be lower than this by 2 or 3 mm.; however, this problem, while needing investigation, is ignored here; in any case the order of magnitude of the error is probably insignificant when calculating for average conditions.

carbon dioxide at sea level will be equivalent to the barometric pressure less that due to the 47 mm. of water vapor, therefore at sea level:

$$P_{G_1} = B_1 - 47 = 760 - 47$$

If we now ascend to 40,000 feet where the barometric pressure is 141 mm., the pressure of the gases similarly will be: $P_{G_2} = B_2 - 47 = 141 - 47$. The expansion of the gases in this cavity will be increased therefore in the ratio of

$$\frac{B_1 - 47}{B_2 - 47} = \frac{760 - 47}{141 - 47} = \frac{713}{94} = 7.6$$

and not simply in accordance with the ratio of $\frac{B_1}{B_2} = \frac{760}{141} = 5.4$

However, in a pneumothorax there is not as a rule, room for free expansion of the gases by collapse of the lung. More often there are adhesions so that the gas cannot freely dilate the cavity and as a result the pressure within the pneumothorax increases. This increase in pressure will be inversely proportional to the freedom with which the cavity expands, therefore, in most instances it is the increase in pressure accompanying the increase in volume that produces the harmful clinical effects.

Example 4. An even more complicated condition exists, as pointed out by Behnke and by Dill, in the growth of air bubbles in tissue fluids on rapid ascent to high altitudes. Air bubbles as shown by Boothby and Walsh first become visible to the eye at or around 12,000 feet (483 mm.) in the spinal fluid in the outer limb of a manometer connected to a needle which is introduced into the spinal canal of a human subject. Therefore, it can be presumed that bubbles begin to form in the fluid in the spinal canal and in other body fluids at about the same barometric pressure. On formation the bubble is composed not only of nitrogen but will also be in equilibrium with the partial pressure of carbon dioxide, oxygen and water vapor in the tissues. The partial pressure of oxygen and carbon dioxide are maintained essentially constant in the tissues as is the pressure of water vapor.

At B_1 = 483 mm. (12,000 feet) let us assume with the subject breathing oxygen the tissue $P_{CO_2} = 50$, the $P_{O_2} = 25$ and the $P_{H_2O} = 47$. In consequence, the $P_{N_2} = B_1 - (50 + 25 + 47) = B_1 - 122 = 483 - 122 = 361$. On proceeding to higher elevations this nitrogen part of the gas bubble will enlarge as the barometric pressure decreases; and into this expanding bubble not only water vapor but also carbon dioxide and oxygen of the body fluids will diffuse because unlike the nitrogen in the tissues, the pressure of carbon dioxide and oxygen remain essentially constant with the subject breathing oxygen as the altitude increases up to 35,000 feet, B_2 = 179 mm. Therefore carbon dioxide and oxygen will, like water vapor, diffuse into the air bubble and maintain approximate equilibrium. The total volume of the gas bubble at 35,000 feet may increase therefore after formation at 12,000 feet in the ratio of the respective barometric pressure less approximately 122 mm. as follows:

$$\frac{B_1 - (50 + 25 + 47)}{B_2 - (50 + 25 + 47)} = \frac{B_1 - 122}{B_2 - 122} = \frac{483 - 122}{179 - 122} = \frac{361}{57} = 6.3$$

That is, a bubble which has a volume sufficient to become visible at 12,000 feet will without the migration into it of any more nitrogen molecules be 6.3 times larger when the aviator reaches 35,000 feet; at 40,000 feet with a barometer of 141 mm. the bubble will have made a total increase in size after its formation corresponding to the ratio $\frac{361}{141 - 122} = 19$. In other words, going an additional 5,000 feet from 35,000 ft. to 40,000 ft. triples the volume of the air bubble from the diffusion into it of carbon dioxide, oxygen and water vapor. As mentioned, the bubble first became visible at 12,000 ft. and the carbon dioxide and oxygen, especially the carbon dioxide, probably plays a large part in the birth of the bubble and will enter into the probability calculation of Piccard who for simplicity limited his exposition to nitrogen; this is likely because of the relatively large number of carbon dioxide molecules, loosely combined with base, present in tissue fluids as compared with nitrogen molecules free in solution equilibrium.

However, as the subject is breathing oxygen and in consequence the nitrogen in the blood stream will be quickly washed out, there will be a progressive decrease of the nitrogen not only in the tissues but possibly also in the bubble. At the present time there is no means of determining the rate at which nitrogen will diffuse in or out of the bubble after it is once formed and therefore the actual increase in size of the bubble may be slightly different from that given in the example by an unknown amount as the result of the influence of unknown factors.

Example 5. The measurement of the vital capacity is another example which is often erroneously expressed. The vital capacity is actually the change in volume from the expansion of the chest by the greatest possible inhalation to the contraction of the chest by the greatest possible expiration. This volume to represent accurately the movements of the chest must be expressed, therefore in the gas volume corresponding to the body temperature and to the existing barometric pressure with the gas saturated with water vapor at 37° C.

The vital capacity has, however, frequently been erroneously expressed variously either at standard temperature and pressure dry or at the volume as measured either by a wet or dry spirometer at laboratory temperature.

Numerically the volume should be expressed in liters to three significant figures (two decimal points) for example 4.83 liters and not 4830 cubic centimeters as the latter indicates an accuracy of four significant figures which is impossible to obtain.

To prevent errors of considerable magnitude, especially at high altitudes, it is necessary to know accurately the temperature and barometric pressure at which the vital capacity is measured. Also it is necessary to have the gases <u>completely</u> saturated with water vapor at the measuring temperature, therefore, the measurement of the volume must be over water by means of a wet meter or water float gasometer. If a dry meter or dry bellows type of spirometer is used it is most difficult to determine the degree to which the gases are saturated as obviously they cannot be considered completely saturated unless liquid water is present.*

As it is usually desirable to have both the S.T.P.D. value and the ambient alveolar value, the observed volumes should first be reduced to 0° C., 760 mm. barometric pressure and dry; this S.T.P.D. volume is then brought up to the volume, V_L, which the gases would occupy in the lungs at 37° C. and at the ambient barometric

* The CO_2 should not be absorbed. If it is absorbed an error of about -2 % is produced at ground level which increases to about - 21 % at 40,000 feet.

pressure less 47 mm. for water vapor. The calculation* should be carried out in two stages as there is less likelihood of careless errors creeping in:

$$(1)\quad V_{stpd} = V_o \times \frac{273}{273 + T_o} \times \frac{B_o - P_{w_o}}{760}$$

$$(2)\quad V_L = V_{stpd} \times \frac{273 + 37}{273} \times \frac{760}{B_o - 47}$$

If desired, however, the two equations can be combined so as to omit the intermediate calculation of the S.T.P.D. value as follows:

$$(3)\quad V_L = V_o \times \frac{\cancel{273}}{273 + T_o} \times \frac{B_o - P_{w_o}}{\cancel{760}} \times \frac{273 + 37}{\cancel{273}} \times \frac{\cancel{760}}{B_o - 47}$$

$$(4)\quad V_L \quad V_o \times \frac{273 + 37}{273 + T_o} \times \frac{B_o - P_{w_o}}{B_o - 47}$$

V_o = the volume as observed in water gasometer at T_o
T_o = the temperature of the gas in the water gasometer at time of reading V_o
B_o = the barometric pressure at time of reading V_o
V_{stpd} = the volume V_o after correcting it to 760 mm. 0° C. dry
V_L = the volume V_o taken to ambient barometer, B_o, 37° C. and saturated and therefore represents the true expansion of the lungs from complete expiration to complete inspiration, that is, the vital capacity.
47 = the value accepted by physiologists as representing the vapor pressure of body fluids at body temperature. Its true value may vary slightly from this under various body conditions.

Eckman and Barach (Jour. Aviation Med. 13:37, 1942, March) call attention to the importance of making allowance for water vapor, temperature and barometric pressure in calculating the vital capacity of the lungs. Unfortunately, they are in error in the last factor of their equation when they subtract the water vapor corresponding to T_o from the vaper pressure of water corresponding to 37° C. Their formula $V_L = V_o \times \frac{310}{273 + T_o} \times \frac{B_o}{B_o - (47 - P_{w_o})}$ is not correct and causes an error of nearly 3 per cent at 40,000 feet.

Example 6. Addition of nitrogen to the air in a room, chamber or gasometer is often used to simulate altitude instead of low pressure chambers. Sometimes results have been obtained when using nitrogen that seem to be different from those obtained in the low pressure chamber. Usually, however, the simulated altitude is improperly calculated due usually to failure to handle the water vapor correctly. The following illustrates in three stages how the simulated altitude should be calculated. All pressures are expressed in millimeters of mercury. The term "tracheal air" is used arbitrarily to indicate atmospheric air saturated with moisture at body temperature which is the actual condition of the air as it enters the alveoli before any exchange with blood gases has occurred. This is, of course, an arbitrary division because gas exchange proceeds more or less simultaneously with saturation. The word "trachea" does not have an anatomical limitation but, as mentioned above, is used arbitrarily.

* A convenient set of factors for making these calculations is given in Table I.

A. The partial pressure of oxygen in the tracheal air at any altitude is obtained from the equation:

$$(PT_{O_2})_a = (B_a - 47) \times 0.2093$$

Where: $(PT_{O_2})_a$ = partial pressure of oxygen in the tracheal air at any altitude.
B_a = total barometric pressure at the altitude.
47 = water vapor pressure of saturated air at 37° C.
0.209 = volumetric fraction of oxygen in atmospheric air (dry).

B. The partial pressure of oxygen in the tracheal air when using nitrogen to simulate altitude is obtained from the equation:

$$(PT_{O_2})_g = (B_g - 47) \times f_{O_2}$$

Where: $(PT_{O_2})_g$ = partial pressure of oxygen in tracheal air obtained at ground level by simulating altitude by addition of nitrogen.
B_g = total barometric pressure at ground level.
47 = water vapor pressure of saturated air at 37° C.
f_{O_2} = volumetric fraction of oxygen in the chamber air (dry) after nitrogen has been added.

C. In order to compare the results obtained between an altitude simulated by nitrogen with those actually obtained by altitude or by utilizing a negative pressure chamber, the two expressions may be equated and then solved for B_a which would be the actual barometric pressure for an altitude corresponding to the nitrogen added.

Equating the two equations:

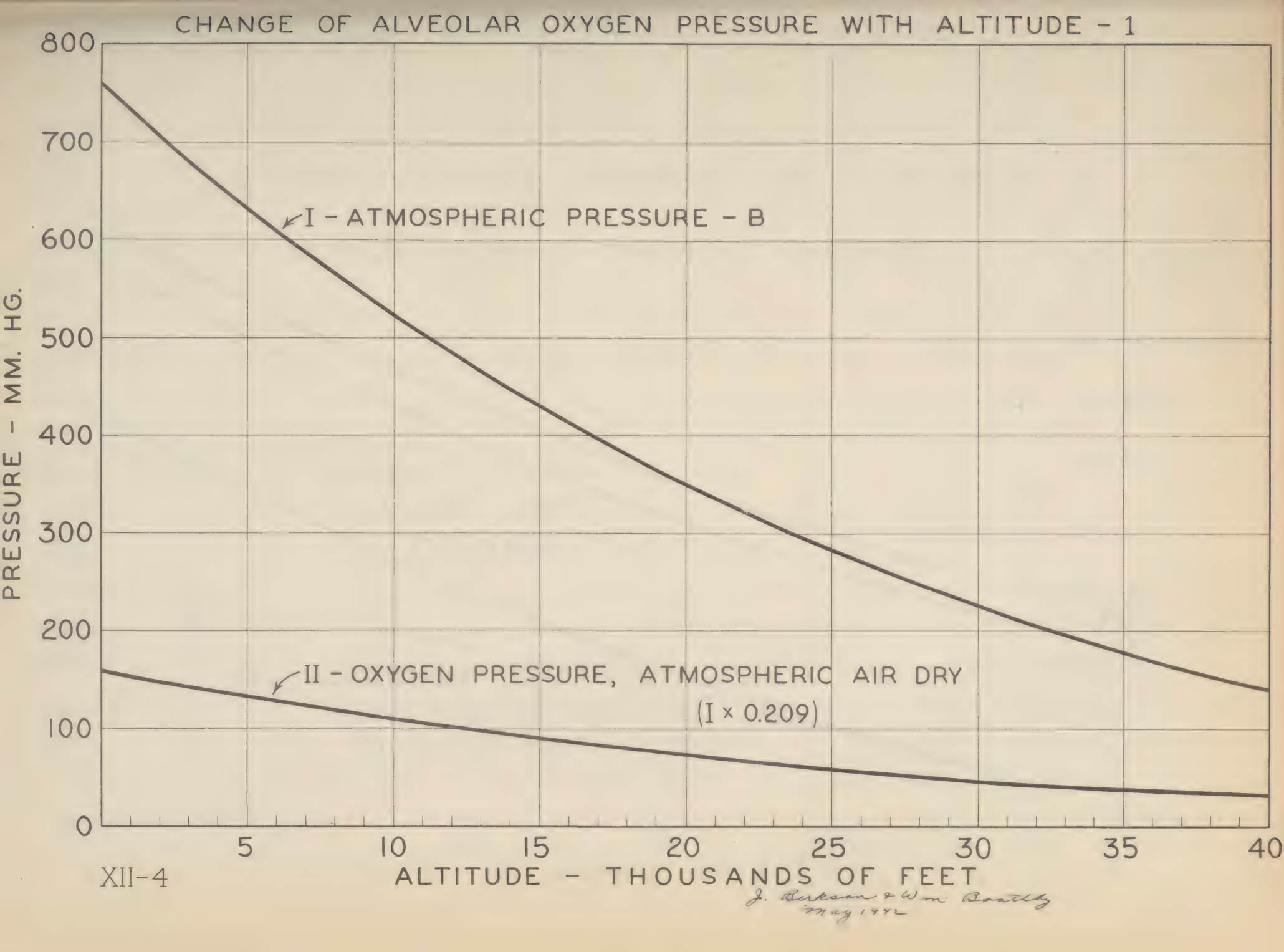
$$(B_a - 47) \times 0.209 = (B_g - 47) \times f_{O_2}$$

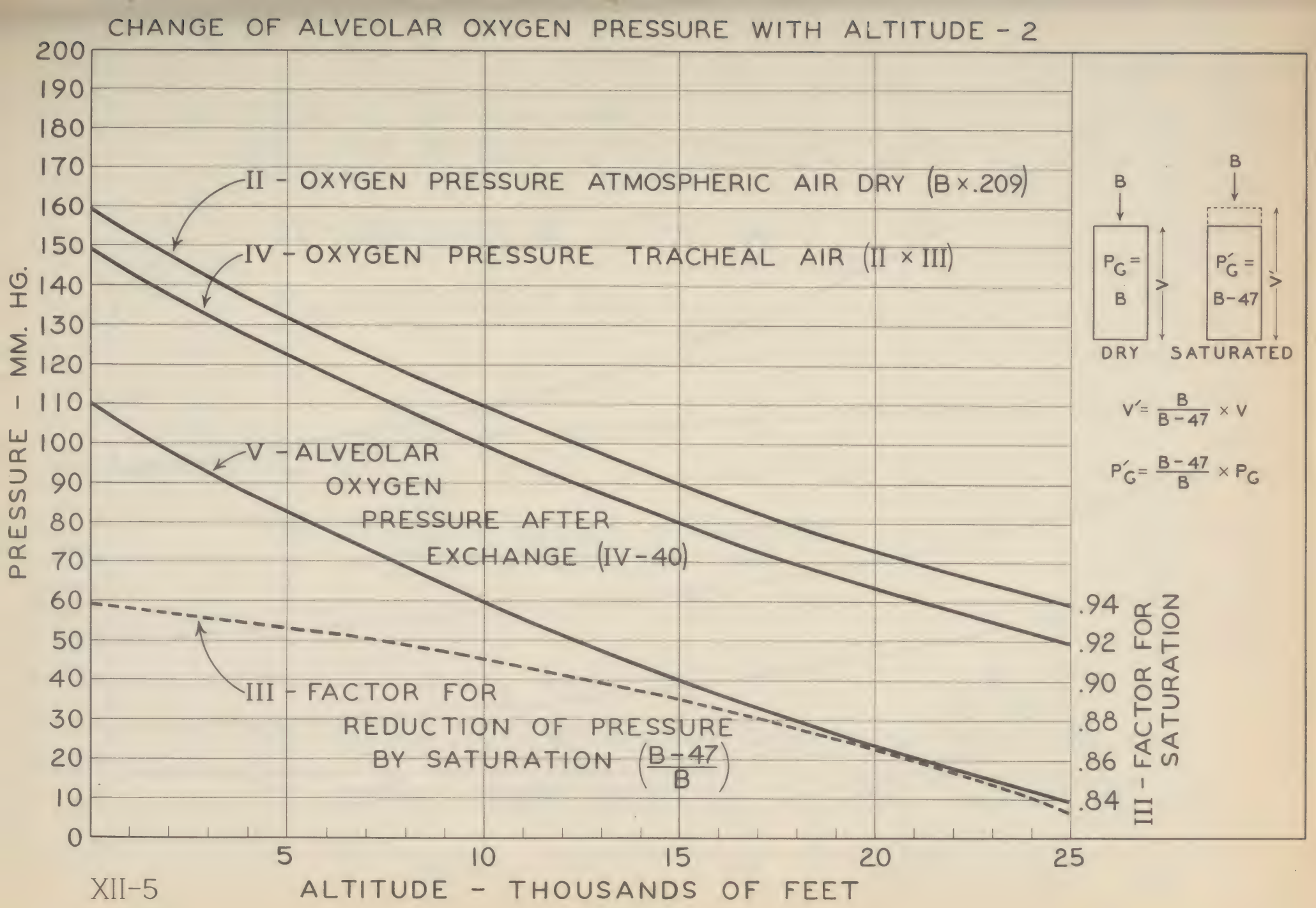
Solving for B_a

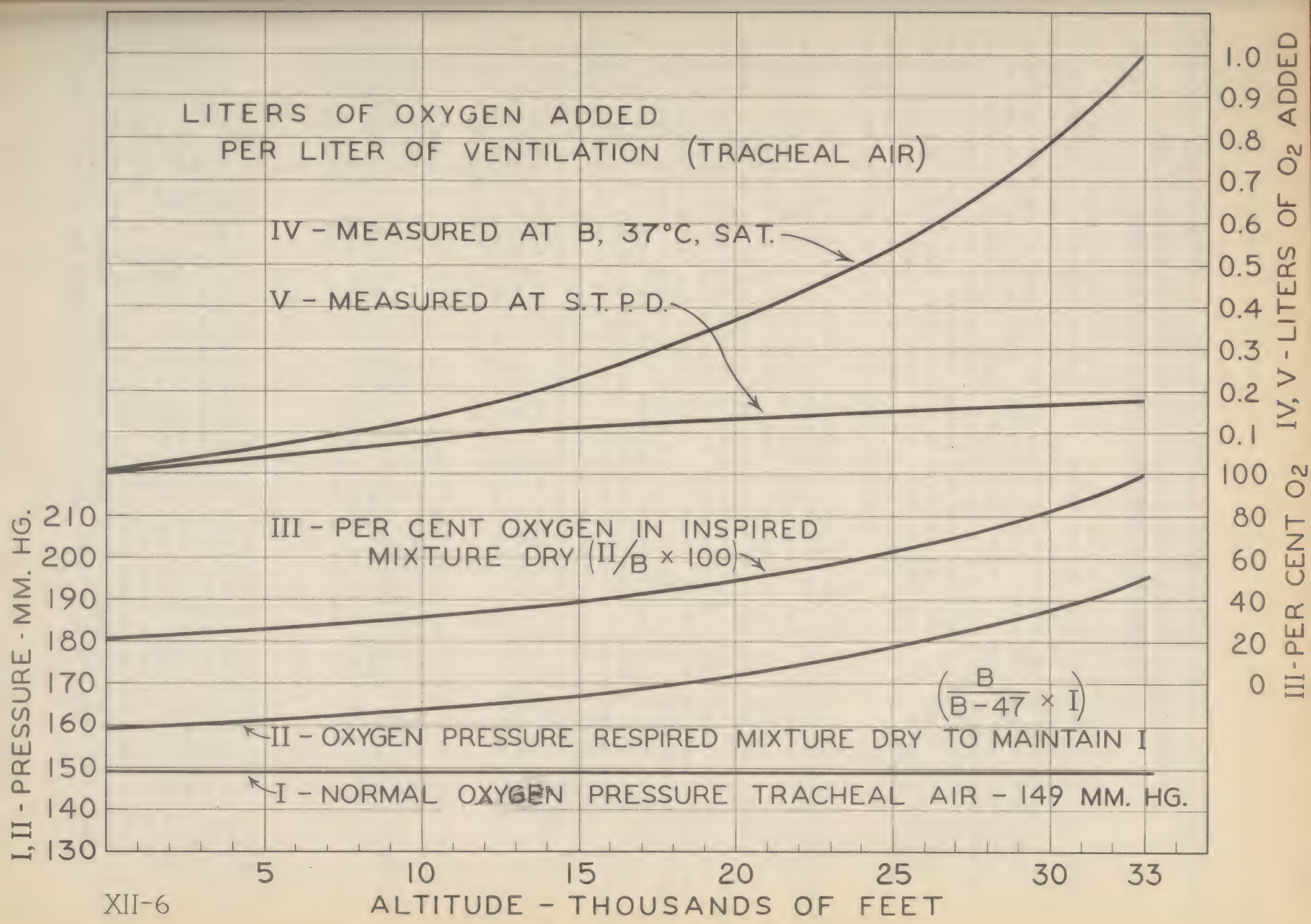
$$B_a = \frac{(B_g - 47) \times f_{O_2}}{0.209} + 47 \text{ or } B_a = (B_g - 47) \frac{f_{O_2}}{0.209} + 47$$

It is to be noted specifically that this method in both instances deals properly and simply with the partial pressure of water vapor which is constant at 47 mm. of Hg in the lungs under all conditions.

From the barometric pressure thus obtained one looks up in the "Altitude-Pressure Tables Based on the United States Standard Atmosphere" the corresponding altitude in feet.


CHANGE OF ALVEOLAR OXYGEN PRESSURE WITH ALTITUDE - 1
800
700
600
500
400
300
200
100
0
PRESSURE - MM. HG.
I - ATMOSPHERIC PRESSURE - B
II - OXYGEN PRESSURE, ATMOSPHERIC AIR DRY
(I x 0.209)
5
10
15
20
25
30
35
40
ALTITUDE - THOUSANDS OF FEET
XII-4
J. Berkson & Wm. Bantly
May 1942


CHANGE OF ALVEOLAR OXYGEN PRESSURE WITH ALTITUDE - 2
PRESSURE - MM. HG.
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
II - OXYGEN PRESSURE ATMOSPHERIC AIR DRY (B x .209)
IV - OXYGEN PRESSURE TRACHEAL AIR (II x III)
V - ALVEOLAR OXYGEN PRESSURE AFTER EXCHANGE (IV-40)
III - FACTOR FOR REDUCTION OF PRESSURE BY SATURATION (B-47)/B
B
$P_G = B$
V
DRY
B
$P'_G = B-47$
V'
SATURATED
$V' = \frac{B}{B-47} \times V$
$P'_G = \frac{B-47}{B} \times P_G$
.94
.92
.90
.88
.86
.84
III - FACTOR FOR SATURATION
5
10
15
20
25
ALTITUDE - THOUSANDS OF FEET


LITERS OF OXYGEN ADDED
PER LITER OF VENTILATION (TRACHEAL AIR)
IV - MEASURED AT B, 37°C, SAT.
V - MEASURED AT S.T.P.D.
III - PER CENT OXYGEN IN INSPIRED
MIXTURE DRY (II/B × 100)
(B/(B-47) × I)
II - OXYGEN PRESSURE RESPIRED MIXTURE DRY TO MAINTAIN I
I - NORMAL OXYGEN PRESSURE TRACHEAL AIR - 149 MM. HG.
I, II - PRESSURE - MM. HG.
210
200
190
180
170
160
150
140
130
III - PER CENT O2
100
80
60
40
20
0
IV, V - LITERS OF O2 ADDED
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
5
10
15
20
25
30
33
ALTITUDE - THOUSANDS OF FEET

Part II. The Role Played by the Combustion or Respiratory Quotient, Hyperventilation and Diffusion of Gases in the Final Gaseous Equilibrium in the Pulmonary Alveoli Resulting in the Alveolar Ratio

If we know the partial pressure of the carbon dioxide in the alveoli, we may calculate at least approximately the uncompensated partial pressure of the oxygen in the alveoli for any altitude if the person is breathing air provided we make certain assumptions in regard to the alveolar CO_2 and the respiratory quotient, even if we neglect certain other rather important factors. We shall suppose first that the "respiratory quotient" is unity. The oxygen which is removed from the alveoli into the blood is used eventually by various working tissues for combustion, that is oxidation, to supply the necessary energy for these working tissues. The oxygen combines with substances that function as fuel for the body, and there is produced as a result carbon dioxide by combination of the oxygen with the carbon of these substances. The "respiratory quotient" (R.Q.) is the ratio of the volume of carbon dioxide produced to the volume of oxygen consumed.

If the substance which is burned as fuel is carbohydrate, there will be exactly as much carbon dioxide produced in volume as there is oxygen consumed because carbohydrate is composed of a certain number of carbon atoms each combined with two atoms of hydrogen and one of oxygen. During combustion the two atoms of hydrogen combine with the one of oxygen to form water, and there is left over one atom of carbon which combines with the one molecule, composed of two atoms, of oxygen obtained from respiration, to form one molecule of carbon dioxide. Thus, for every molecule, O_2, of oxygen utilized, one molecule, CO_2, of carbon dioxide is produced. Since in a gas equal numbers of molecules occupy the same volume at any particular temperature and pressure, the volume of carbon dioxide produced is the same as the volume of oxygen consumed, and therefore, when carbohydrate (sugar, starch) is the substance which is utilized for combustion the respiratory quotient approximates unity. Hence the alveolar air after exchange will have had added to it as much carbon dioxide as oxygen has been removed. Since there has been no change in the total volume, this means that the partial pressure of the oxygen will be decreased during exchange by the same amount as the pressure of the carbon dioxide is increased. Knowing this we may calculate easily what will be the uncompensated alveolar oxygen pressure at any altitude under these conditions.

We have seen at an altitude at which the atmospheric pressure is B, the partial pressure of the oxygen, p_{O_2}, in the tracheal air is (B - 47) 0.2093. During exchange, carbon dioxide will accumulate in the alveoli to a pressure of say 40 mm. and the partial pressure of oxygen in the alveoli after exchange (alveolar oxygen tension p'_{O_2}) is given under these circumstances when the respiratory quotient is unity, if certain other factors are neglected, as follows:

$$p'_{O_2} = P_{O_2} - p'_{CO_2} = \left[(B - 47)\ 0.2093\right] - 40$$

The respiratory quotient will be less than unity if protein (R.Q. = 0.82) or fat (R.Q. = 0.71) rather than carbohydrate is utilized for combustion. The hydrogen and oxygen contained in these substances exist in a proportion of more than two atoms of hydrogen to one of oxygen; that is, there is an excess of hydrogen atoms compared with water (H_2O). During combustion some of the oxygen that is obtained from respiration is utilized to combine with those extra atoms of hydrogen to form water, and the rest of the oxygen that is utilized combines with carbon to form carbon dioxide as before. Thus, because some of the oxygen is used for the formation of water and does not appear as carbon dioxide, there will be formed less carbon

dioxide than there will be oxygen used and the respiratory quotient will be less than unity. Since more oxygen in volume is utilized than carbon dioxide produced, the total volume of the gases after exchange has taken place is less than the volume before exchange; the size of the difference will depend on how much fat is burned as this forms less carbon dioxide than oxygen utilized, therefore, the respiratory quotient approaches 0.71.

The respiratory quotient will fluctuate ordinarily between 1 and 0.7, but is usually about 0.82 though in special conditions it will go outside of these ranges. To calculate the ratio of the carbon dioxide produced to the oxygen consumed, we need to know the ratio of the volume of the respired air after exchange to the volume of the same air before exchange because technically one collects, measures and analyzes the expired air and not the inspired air.

This ratio of volumes can be calculated from a knowledge of the relative amount of nitrogen present. Since nitrogen does not take part in the metabolic exchange, the amount (number of molecules) of nitrogen is the same before and after exchange. Therefore, if the total volume of inspired air decreases, the fraction of nitrogen contained will increase and in the same proportion. If V is the volume of inspired air before exchange, V' the volume after exchange, f_n, f_{CO_2}, f_{O_2} the fractions respectively of nitrogen, carbon dioxide and oxygen before exchange, f'_n, f'_{CO_2} the corresponding fractions after exchange, then

$$\frac{V}{V'} = \frac{f'_n}{f_n} \text{ or } V = V' \frac{f'_n}{f_n}$$ (Valid for steady state only)

This correction factor must be used to calculate correctly the carbon dioxide produced, the oxygen consumed and the true respiratory or combustion quotient. The details of this calculation follow at end of article.

The alveolar oxygen and carbon dioxide pressure and the alveolar ratio.

However, in aviation it is not entirely the combustion or respiratory quotient that influences the partial pressure of oxygen in the alveoli, because the pressure of carbon dioxide and oxygen in the alveoli as well as the relationship between them - the alveolar ratio - depends on the following factors: (1) the rate and depth of the respiration, that is, the intensity and duration of hyperventilation. (2) on the amount of carbon dioxide produced in relation to the amount of oxygen absorbed, that is, on the true respiratory or combustion quotient, which produces a larger or smaller decrease in the volume of the expired air from that of the inspired air, and (3) the difference in the rate of diffusion of carbon dioxide outward and of oxygen inward. Variations in the predominance of these three factors will tend to make any calculations based on the analysis of a single alveolar air sample differ somewhat from the calculations based on the analysis of expired air collected over a considerable period of time.

In aviation we would whenever possible determine the oxygen and carbon dioxide pressures in alveolar air directly but this is not always possible. However, during the last four years we have made many such analyses with the subject breathing air while gradually ascending from ground level (1000 feet at Rochester) to 20,000 feet and a few experiments up to 22,000 feet in a carefully controlled low pressure chamber. The results thus obtained are very consistent and therefore instructive.

charts
The data shown in/I-1, I-2, I-3, I-4, I-6 and XII-7 indicated that there was a definite, even progressive, decrease in the alveolar oxygen pressure up to a barometric pressure equivalent of about 12,000 feet and that above this level there

was a definite change in that the data no longer could be represented by a straight line but instead gradually curved to the right; there was a corresponding fall in the carbon dioxide curve beginning at the same point indicating that at this level a sufficient degree of anoxia developed to cause hyperventilation.

The first or straight part of this curve was particularly interesting and instructive because it could be calculated with considerable accuracy by the following simple formula:

$$\text{Alv. } P_{O_2} = (B - 47)\ .2093 - (O_2 \text{ absorbed in mm.})$$

However, as the oxygen absorbed was unknown, Boothby and Benson suggested that it could be estimated by taking an average value for carbon dioxide and dividing this by an average R.Q. Doing this we found that a curve constructed by assuming a carbon dioxide of 40 mm. and an R.Q. of 1.0 or a carbon dioxide of 37 mm. and an R.Q. of 0.87 would fit the data very closely in various series of experiments between ground level (1000 feet) and an elevation of about 13,000 feet, but above this level the data could no longer be represented by a straight line.

Boycott and Haldane (Jr. Physiol., 35:355-377, 1908) had shown that on a range of four atmospheres from about 3 3/4 atmospheres to 3/4 of an atmosphere, both the alveolar carbon dioxide and the alveolar oxygen could be represented by a straight line; the alveolar carbon dioxide remained constant around 39 mm. and the alveolar oxygen progressively and evenly decreased.

The fact that the alveolar oxygen can be predicted with considerable accuracy if we make a few assumptions based on average findings has recently been confirmed in a series of 240 experiments made at the Mayo Aero Medical Unit at barometric pressure varying from 3½ atmospheres down to ½ an atmosphere. This data is shown in Chart XII-7.

From our data, if all experimental values obtained at barometric pressures in excess of 500 mm. are used, it is found that the average alveolar oxygen pressure of the data can be predicted with greater accuracy from the average alveolar carbon dioxide pressure and the average <u>alveolar ratio</u> instead of the average <u>respiratory quotient</u> as follows:

$$\text{Mean } p'_{O_2} = (B - 47)\ 0.2093 - \frac{\text{Mean } p'_{CO_2}}{\text{Mean A.R.}}$$

Where Mean A.R. $= \dfrac{\text{Mean } p'_{CO_2}}{.2093\ (B - 47) = p'_{O_2}}$ which represents what is frequently referred to by Haldane as the uncorrected respiratory quotient. It is to be noted that Boothby, Lovelace and Benson erred slightly in using the true combustion or respiratory quotient instead of the uncorrected respiratory quotient or, as we prefer to call it, the alveolar ratio.

Let us discuss the data summarized in figure 4 in some detail at a few significant barometric pressures.

Example 1. At a pressure of 3.5 atmospheres where B = 2660 mm., the alveolar carbon dioxide P_{CO_2} = 37 mm. and the average alveolar ratio is 0.8 (the average of all experiments above 500 mm. was 0.778), the amount of decrease in the oxygen pressure can be calculated by dividing $\frac{37}{.8} = 46$.

Therefore, we deduct the water vapor and proceed as follows:

$$B = 2660$$

$$P_{H_2O} = \frac{47}{2613} \times .2093 = 557 - 46 = 511 = p_{O_2}$$

$$37 = p_{CO_2}$$

$$\underline{2065 = p_{N_2}}$$

$$2613 + 47 = 2660 = B$$

The figure of 511 mm. for p_{O_2} corresponds to that actually found by alveolar air samples.

Example 2. At sea level the calculation is as follows:

A.R. = 0.8 p_{CO_2} = 37. The decrease in oxygen pressure = $\frac{37}{.8} = 46$

$$B = 760$$

$$P_{H_2O} = \frac{47}{713} \times .2093 = 149 - 46 = 103\ p_{O_2}$$

$$37\ p_{CO_2}$$

$$\underline{573\ p_{N_2}}$$

$$713 + 47 = 760 = B$$

Example 3. Next let us examine by three different assumptions the results obtained at 15,000 feet, B = 429 which is an important level because it is only 2000 to 3000 feet above the point where anoxia begins to make the aviator hyperventilate.

A. First we calculate on the assumption that the main factor influencing the A.R. is the combustion factor and that there is no hyperventilation and that therefore the A.R. is still 0.8 and the alveolar p_{CO_2} is still 37 mm. and therefore the oxygen decrease = $\frac{37}{.8} = 46$.

$$B = 429$$

$$P_{H_2O} = \frac{47}{382 \times .2093 = 80 - 46 = 34\ p_{O_2}}$$

$$37\ p_{CO_2}) \text{ No hyperventilation}$$

$$\underline{311\ p_{N_2}}$$

$$382 + 47 = 429 = B$$

However, a p_{O_2} of 34 mm. does not agree with the actual observation in this series of experiments nor in other series of a similar nature. What is the difficulty? It lies in the fact that the subject is hyperventilating and this reduces the alveolar p_{CO_2} to 32 mm. and the alveolar ratio is necessarily definitely elevated because this is an acute rapid elevation in an airplane and the subject is still blowing off carbon dioxide as will be illustrated in the next example.

B. Therefore, with the alveolar p_{CO_2} decreased to 32 mm. and with the A.R. increased to 1.0 the oxygen decrease = $\frac{32}{1}$ = 32 mm.

In consequence: B = 429

$$P_{H_2O} = \frac{47}{382} \times .2093 = 80 - 32 = \begin{array}{r} 48\ p_{O_2} \\ 32\ p_{CO_2} \\ 302\ p_{N_2} \\ \hline 382 + 47 = 429 = B \end{array}$$

There is, as a result of the hyperventilation, an elevation of the A.R. and a lowering of the alveolar p_{CO_2} and that therefore the combustion factor no longer is predominant; this produces a very large increase in the alveolar p_{O_2} from 34 mm. to 48 mm. which agrees with the observed data in figure 4. This however is not entirely beneficial and, as we will see, is in part only temporary. If instead of being in an airplane and therefore at the elevation for only a short time, the subject has gone up on a mountain to live, beneficial compensatory effects will gradually develop. These effects are known as acclimatization. Part of this process is that finally the hyperventilation produces a state of equilibrium. The alveolar CO_2 remains decreased at about 32 mm. but the A.R. returns from 1.0 to normal of 0.8 as no more carbon dioxide is being blown off and the main factor influencing the A.R. is again the combustion factor = R.Q. The results of this compensation are shown in the next example.

C. The new acclimatized condition can be represented in part as follows: A.R. = 0.8 and is close to and mainly dependent upon the combustion or true respiratory quotient. P_{CO_2} = 32, which has been decreased by hyperventilation long enough for the entire body fluids to reach equilibrium. The oxygen decrease is $\frac{32}{.8}$ = 40 mm. Therefore:

$$B = 429$$

$$P_{H_2O} = \frac{47}{392} \times .2093 = 80 - 40 = \begin{array}{r} 40\ p_{O_2} \\ 32\ p_{CO_2} \\ 319\ p_{N_2} \\ \hline 382 + 47 = 429 = B \end{array}$$

The factors involved in acclimatization are many and sundry and their discussion cannot be taken up here. However, the first phase of acclimatization includes rather extensive and acute hyperventilation whereby the alveolar p_{CO_2} is lowered; carbon dioxide is washed out and because of the extensive hyperventilation the alveolar p_{O_2} is greatly increased as shown in example B. The second phase of acclimatization as shown in example C begins when equilibrium of the body to the new alveolar p_{CO_2} is reached; the hyperventilation decreases and equilibrium is finally reached with a decreased alveolar CO_2 and normal A.R. and there is therefore partial recession in the alveolar p_{O_2}. In the first stage the alveolar oxygen rises from 34 mm. (example A) to 48 mm. (example B) and in the second stage merely as part of a physical phenomenon recedes about one-half its advance and tends to stabilize around 40 mm. (example C).

This final decrease in alveolar p_{O_2} is more than compensated for by other important compensating factors.

To summarize: (1) In example A where it is assumed the aviator is breathing normally without hyperventilating in an attempt to compensate for the lower partial pressure of oxygen in the inspired air, the alveolar oxygen pressure must necessarily be very low, 34 mm. (2) In example B when there is marked hyperventilation with a decrease in alveolar CO_2 pressure and the A.R. is therefore high, there is a marked elevation in the alveolar O_2 pressure. However, this is accompanied by all the ill effects of an uncompensated lowering of the alveolar CO_2 including a considerable shift in the hemoglobin dissociation curve to the left. (3) In example C. there is a recession in the partial pressure of oxygen and as a result a decrease in the intensity of hyperventilation; although the carbon dioxide remains lowered, the A.R. returns to a normal level corresponding to its normal relation to the respiratory quotient. This is merely one phase of the complicated mechanism of acclimatization to high altitude and does not occur in aviators under ordinary circumstances.

Dill, Christensen and Edwards (Gas Equilibrium in Lungs at High Altitudes: Am. J. Physiol., 1936, 115:537) make the following statement: "Another observation was made which indicates that the occurreme of mountain sickness does not depend closely on the oxygen saturation of arterial blood. In several individuals arterial blood was drawn soon after arrival at a station and again a week or ten days later. Usually little change was found to occur in saturation although acclimatization had been going on in the meanwhile. In the case of Dill at Montt the saturation on the day of arrival was 73.7 per cent and 9 days later 71.6 per cent. On the second day after arrival he had had typical mountain sickness, but from that time on remained free of symptoms despite the fact that he had had the lowest saturation recorded at the station."

Similar calculations for the data in figure 4 can be made for 18,000 and 20,000 feet. At those elevations the hyperventilation is so great that few individuals can withstand the combined effects of acapnia superimposed on anoxia for more than a short period.

The main value of the data and calculations presented in this paper rests on the fact that it forms a basis from which to calculate the amount of oxygen needed to maintain the alveolar oxygen pressure of the aviator at any desired level by the proper administration of oxygen. The average alveolar oxygen for any altitude up to 12,000 or 13,000 feet has been well established and this will not vary in normal young men up to these altitudes any more than it will at sea level. In fact, its regression with increasing altitude is as constant and predictable over a total of 4 atmospheres as is the constancy of the alveolar p_{CO_2} throughout a similar range of barometric pressure. Between elevations of 12,000 and 20,000 feet by making allowance for hyperventilation the alveolar oxygen pressure as well as that of carbon dioxide can be predicted within 3 or 4 mm.

INSPIRED VOLUME

If V is the volume of respired air before exchange, V' the volume after exchange, f_n, f_{CO_2}, f_{O_2}, the fractions respectively of nitrogen, carbon dioxide and oxygen before exchange, f'_n, f'_{O_2} the corresponding fractions after exchange, then:

$$\frac{V}{V'} = \frac{f'_n}{f_n} \text{ or } V = \frac{f'_n}{f_n} V'$$

The volume of carbon dioxide produced is

$$CO_2 = V'f'_{CO_2} - Vf_{CO_2} = V'f'_{CO_2} - V' \frac{f'_n}{f_n} f_{CO_2} = V' \left(f'_{CO_2} - f_{CO_2} - \frac{f'_n}{f_n}\right)$$

The volume of oxygen consumed is

$$O_2 = Vf_{O_2} - V'f'_{O_2} = V' \frac{f'_n}{f_n} fO_2 = V'f'_{O_2} = V'\left(f_{O_2} \frac{f'_n}{f_n} - f'_{O_2}\right)$$

The respiratory quotient, which is the ratio of the volume of carbon dioxide produced to the volume of oxygen consumed, is given therefore by

$$R.Q. = \frac{f'_{CO_2} - f_{CO_2} \frac{f'_n}{f_n}}{f_{O_2} \frac{f'_n}{f_n} - f'_{O_2}}$$

When breathing pure air the following values may be substituted

$$R.Q. = \frac{f'_{CO_2} - 0.0003 \frac{f'_n}{0.7904}}{0.2093 \frac{f'_n}{0.7904} - f'_{O_2}}$$

Since the normal proportion of carbon dioxide in the atmospheric air, 0.0003, is small, and since the numerator, f'_n of the fraction $\frac{f'_n}{0.7904}$ does not vary under normal circumstances beyond the limits of 0.81 and 0.78, the fraction does not produce a significant alteration in the term $f'_{CO_2} \frac{f'_n}{f_n}$ unless the value for f_{CO_2} is above 1.0 per cent (0.01).

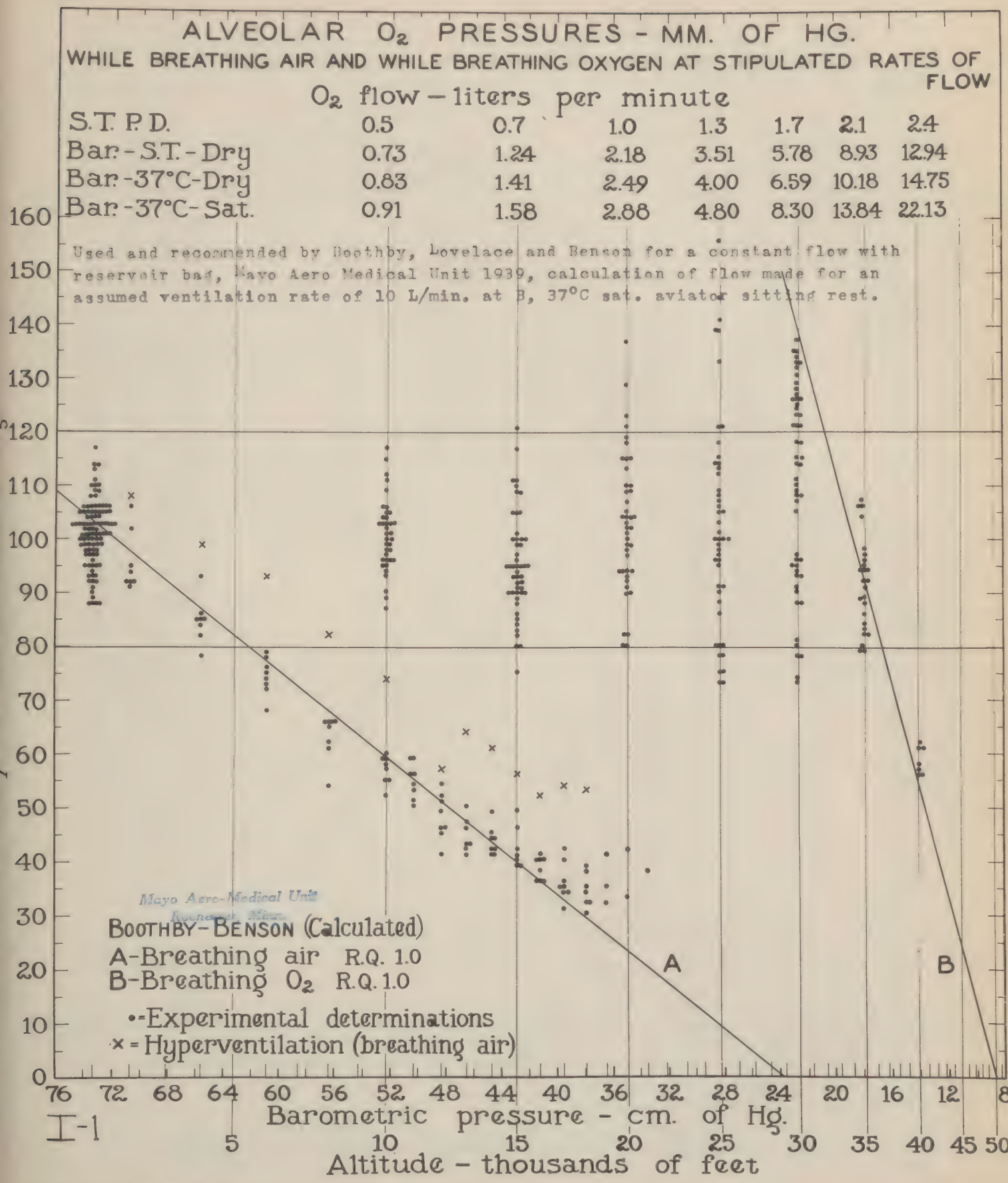
Therefore, when the subject is breathing pure atmospheric air the equation can be simplified as follows:

$$R.Q. = \frac{f'_{CO_2} - 0.0003}{0.2648\ f'_n - f'_{O_2}}$$

That is, the respiratory quotient, when the subject is breathing normal air is the difference between the percentage of carbon dioxide in the expired air and the percentage of carbon dioxide in the inspired air divided by the percentage of oxygen in the inspired air modified by the fraction $\frac{f'_n}{f_n}$ (for change in volume between the inspired and expired air) less the percentage of oxygen in the expired air. It should be noted that the fractional correction for change in volume in the numerator cannot be ignored if the proportion of carbon dioxide in the inspired air exceeds 0.1 per cent.

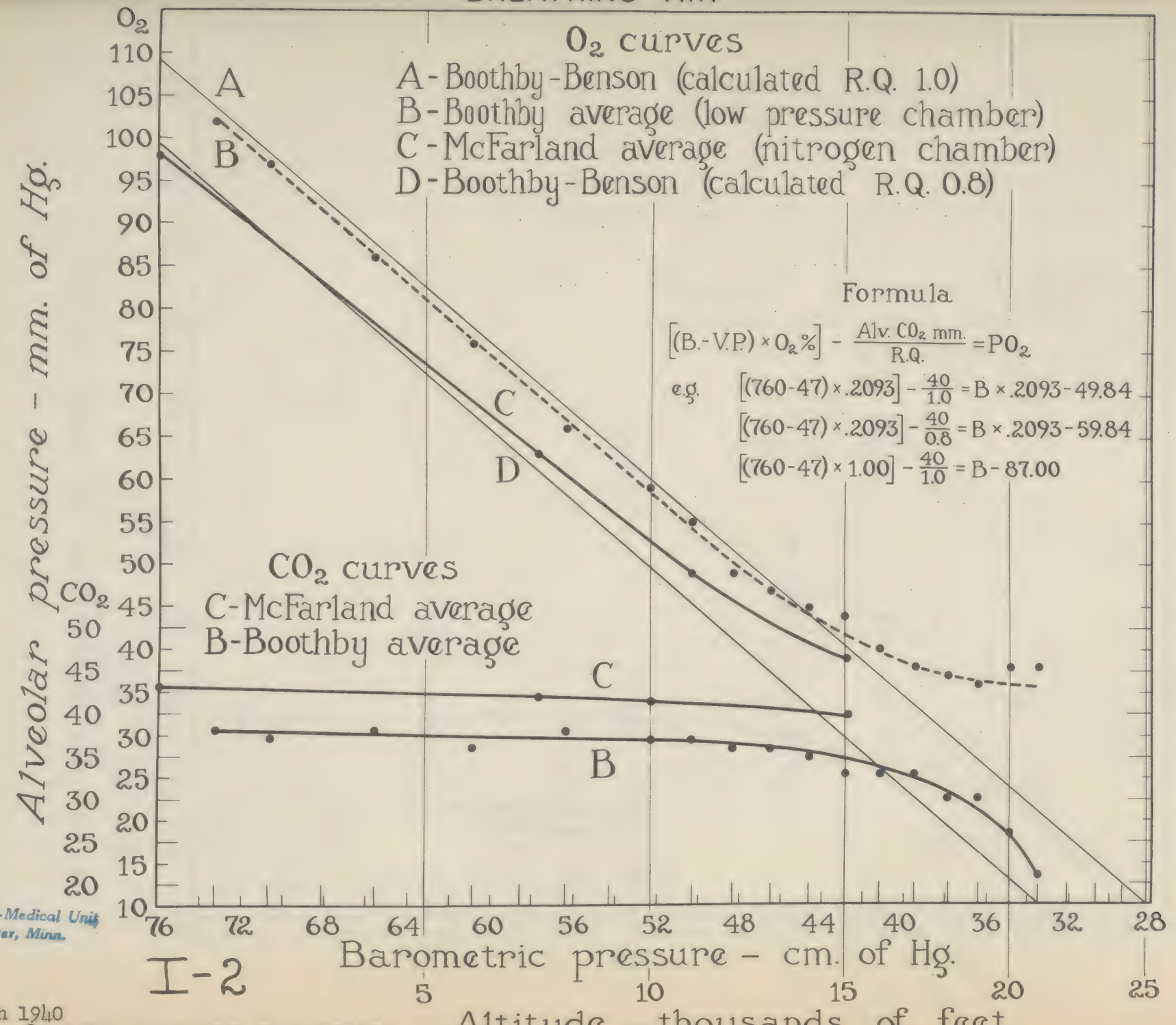
Instead of the fractions of the constituent gases in the foregoing formula for the respiratory quotient, we may write the partial pressures of these same gases.

Subject: High altitude effect on human body
Published: J. Aeronaut. Sc. 7: 465, Sept. 1940



W.M.Beethby, W.R.Levelace and O.O.Benson Jr.

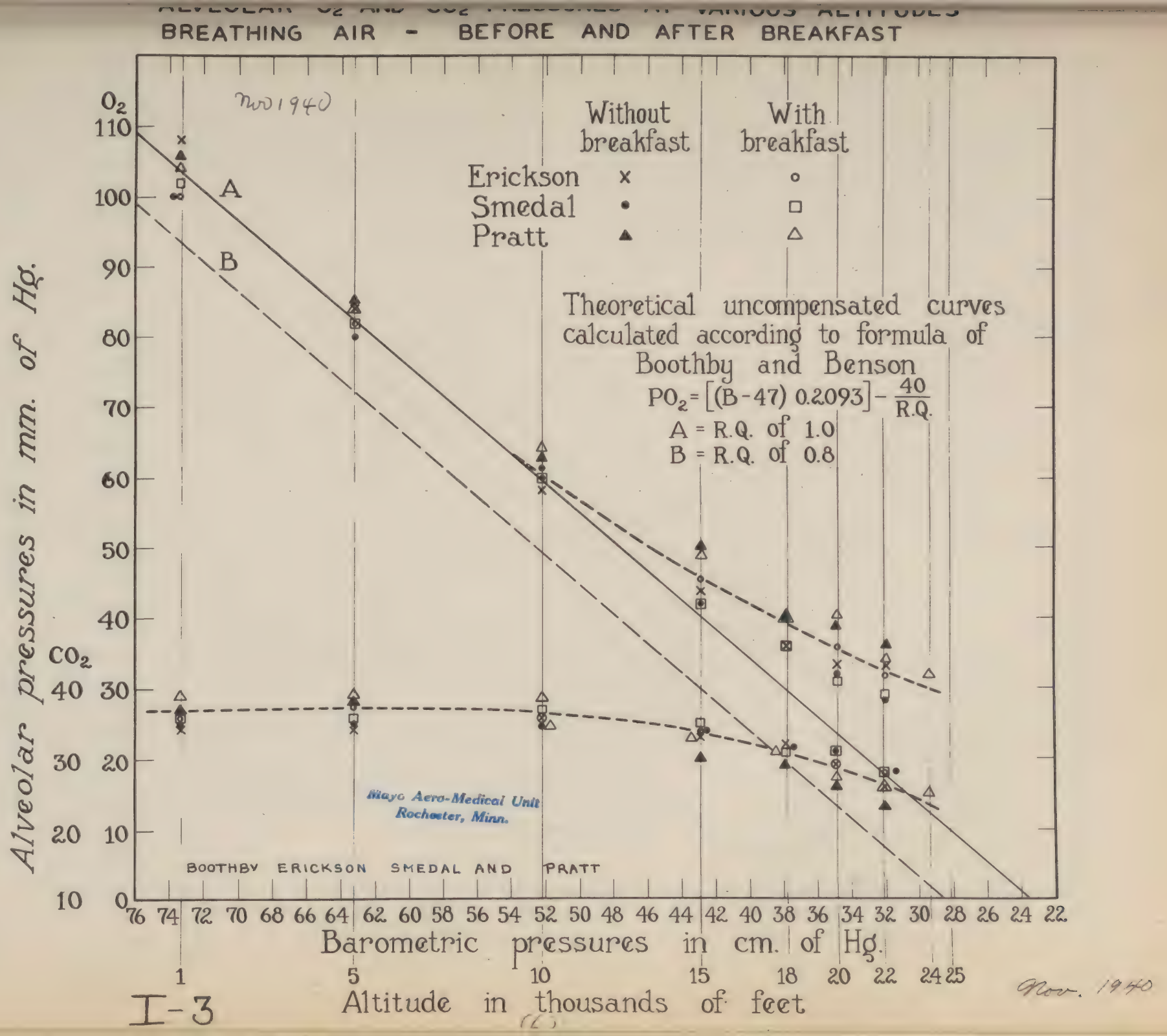
BREATHING AIR

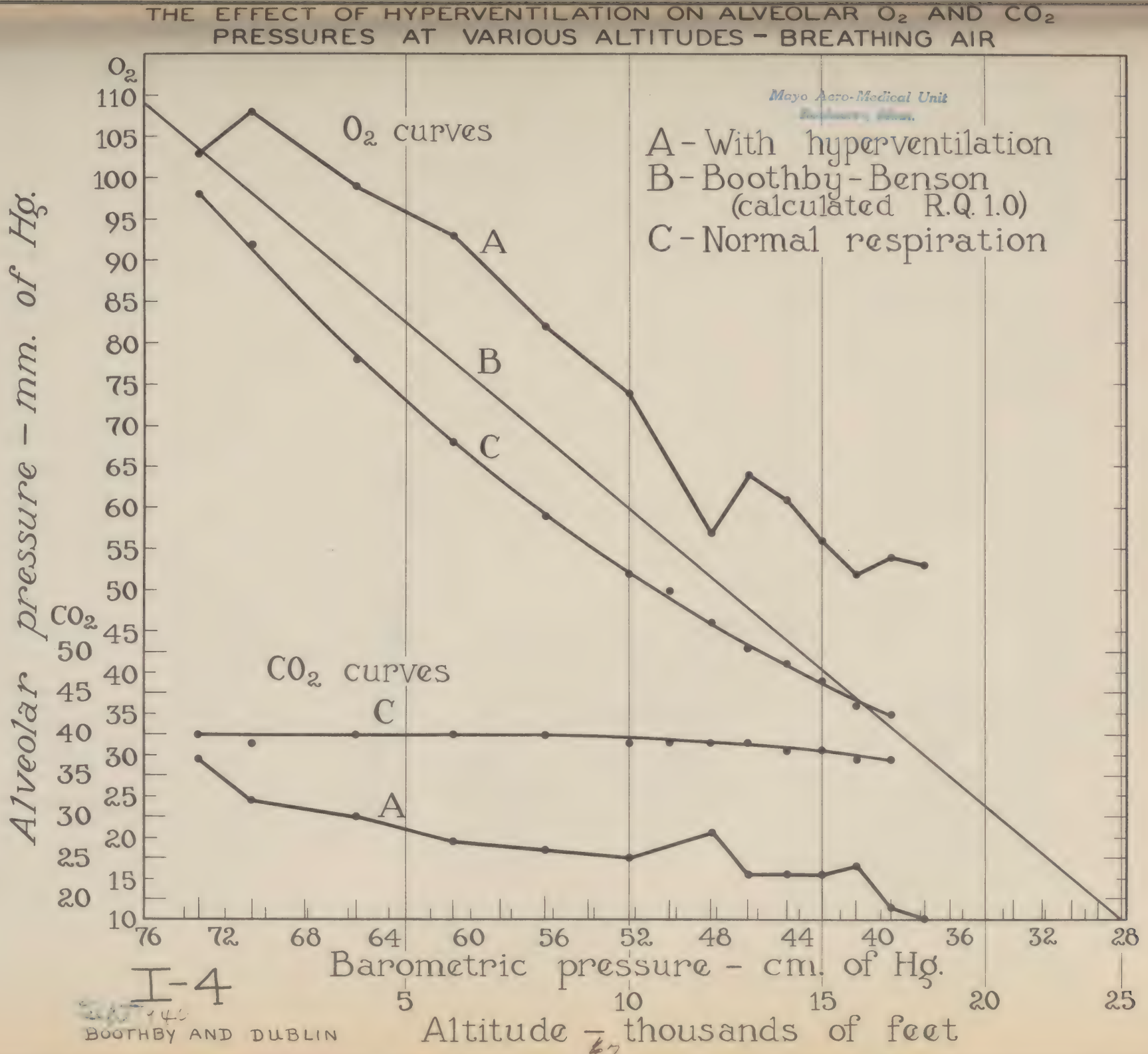


Mayo Aero-Medical Unit
Rochester, Minn.

I-2

March 1940
BOOTHBY LOVELACE AND BENSON


ALVEOLAR O2 AND CO2 PRESSURES AT VARIOUS ALTITUDES
BREATHING AIR - BEFORE AND AFTER BREAKFAST
Nov 1940
Without breakfast
With breakfast
Erickson x o
Smedal • □
Pratt ▲ △
A
B
Theoretical uncompensated curves calculated according to formula of Boothby and Benson
$PO_2 = [(B-47)\ 0.2093] - \frac{40}{R.Q.}$
A = R.Q. of 1.0
B = R.Q. of 0.8
Alveolar pressures in mm. of Hg.
O2
CO2
Mayo Aero-Medical Unit
Rochester, Minn.
BOOTHBY ERICKSON SMEDAL AND PRATT
Barometric pressures in cm. of Hg.
Altitude in thousands of feet
I-3
Nov. 1940

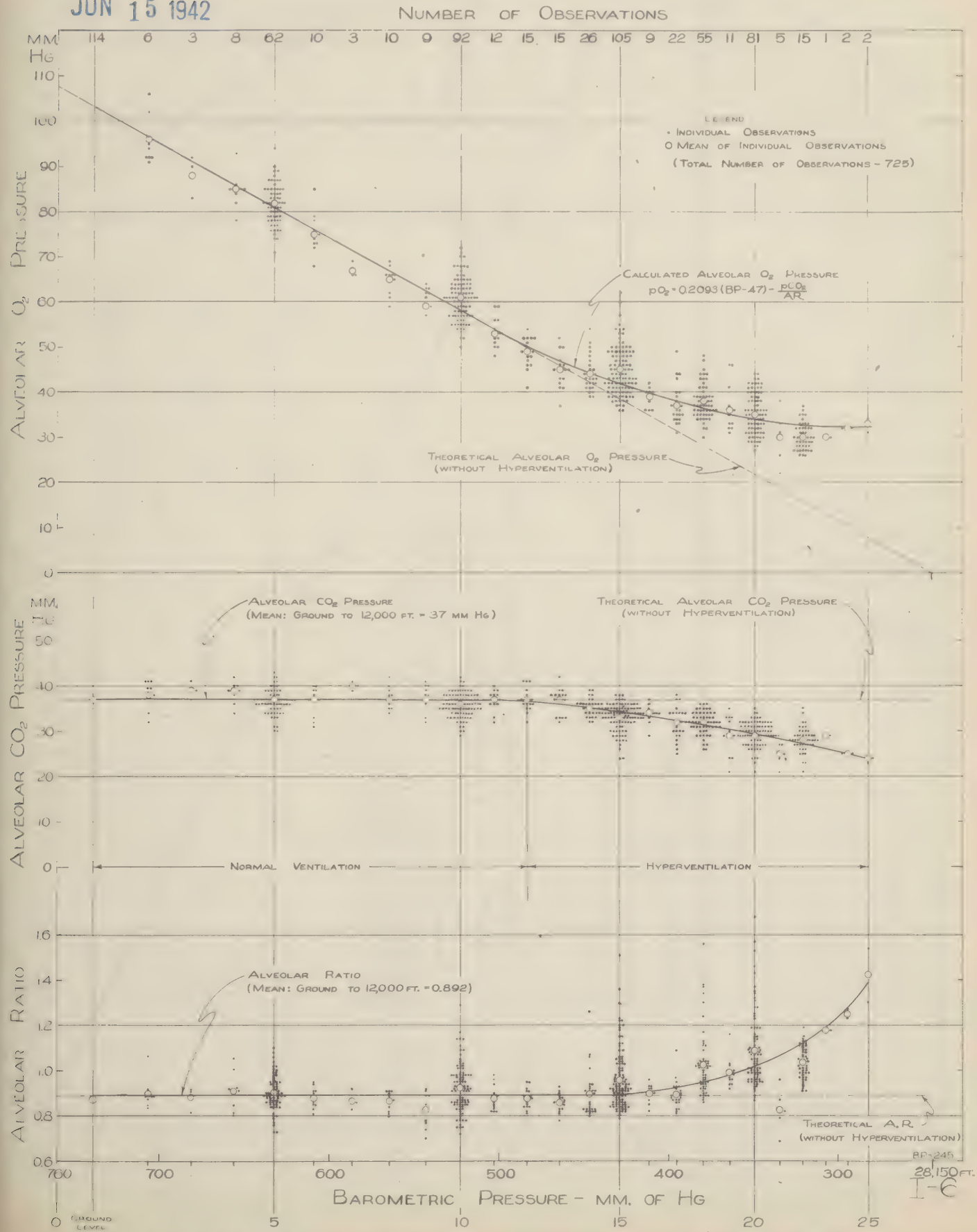


I-4

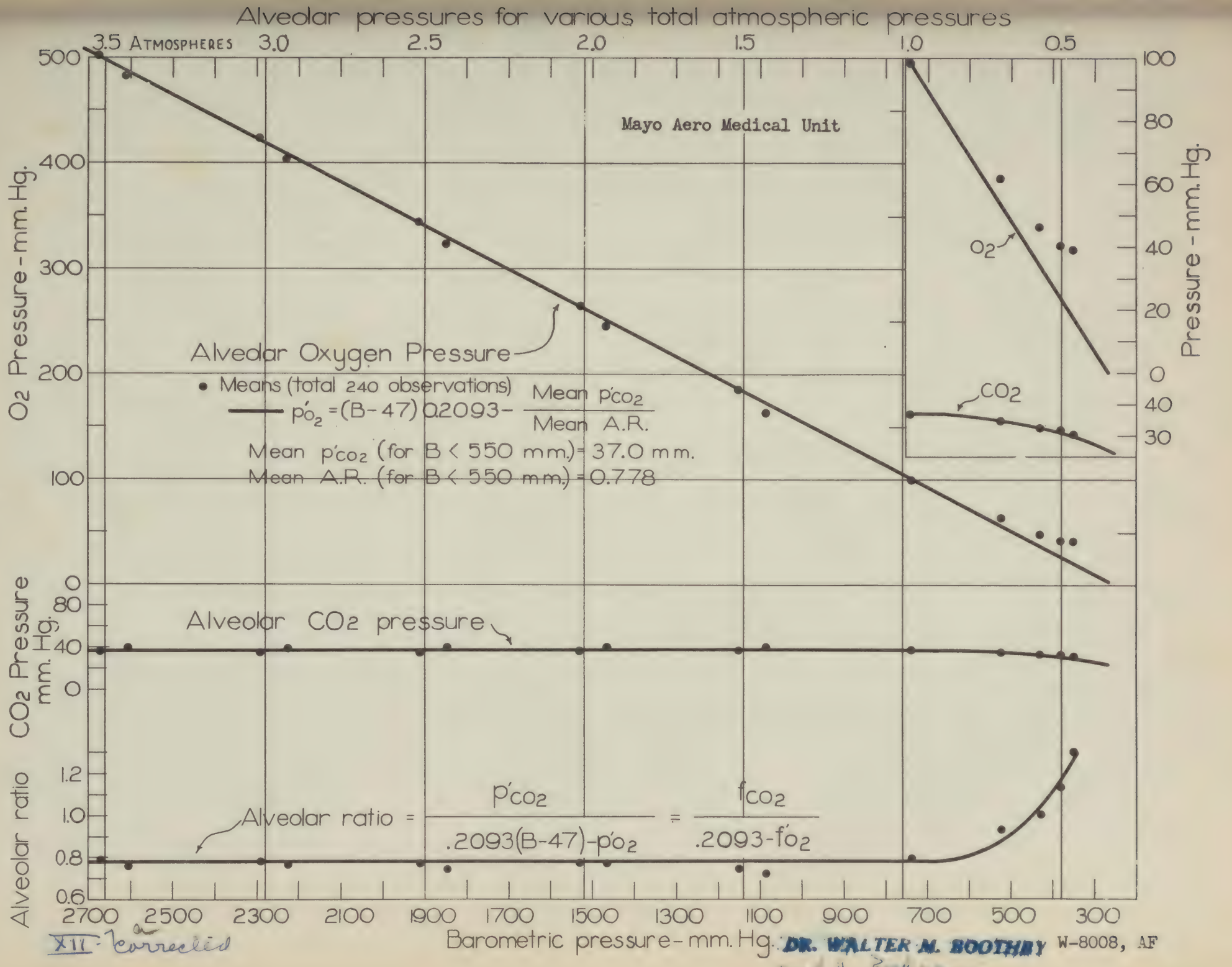
BOOTHBY AND DUBLIN

Alveolar O_2 and CO_2 Pressures and Alveolar Ratio at Various Altitudes while Breathing Air - Rapid Ascent

All Subjects Acclimatized to an Altitude of 1000 feet



Mayo Aero-Medical Unit



XII - Corrected

NATIONAL RESEARCH COUNCIL, DIVISION OF MEDICAL SCIENCES
acting for the
COMMITTEE ON MEDICAL RESEARCH
of the
Office of Scientific Research and Development
COMMITTEE ON AVIATION MEDICINE

Report No. 341
RESTRICTED Date 14 June 1944

ALVEOLAR RESPIRATORY QUOTIENTS; AN EXPERIMENTAL STUDY OF THE DIFFERENCE BETWEEN TRUE AND ALVEOLAR RESPIRATORY QUOTIENTS, WITH A DISCUSSION OF THE ASSUMPTIONS INVOLVED IN THE CALCULATION OF ALVEOLAR RESPIRATORY QUOTIENTS AND A BRIEF REVIEW OF EXPERIMENTAL EVIDENCE RELATING TO THESE ASSUMPTIONS.

From the Mayo Aero Medical Unit, Rochester, Minnesota by J. B. Bateman and Walter M. Boothby.

SUMMARY

Presented at the meeting of the Subcommittee on Oxygen and Anoxia, N.R.C., June 16, 1944

1. Measurements have been made of the resting metabolic rate and the composition of Haldane-Priestley alveolar air from four subjects before and after a meal of rice. Experiments were carried out both at ground level and at 12,000 feet simulated altitude.

2. Comparison of "true" and "alveolar" respiratory quotients reveals the following fact

a.

	Ground level	12,000 feet s.a.
Range of true R.Q. values:	0.704 - 0.930	0.782 - 0.953
Alveolar R.Q. is on the average less than true R.Q. by	0.0155	0.0236
Same in per cent	2	3

b. The small average differences mask considerably larger systematic personal differences and a pronounced tendency for the composition of Haldane-Priestley samples to show a smaller response to changes in true respiratory quotient than would be anticipated from the simple theory.

3. Examination of the tacit assumptions involved in the use of the usual alveolar R.Q formula suggests the following conclusions to be drawn from our experimental data:

a. As an approximate procedure for the establishment of oxygen standards for aviators, the use of the alveolar air equation is justified. This does not imply, however, that for practical purposes the use of the "tracheal" air as a point of reference may not be more convenient.

b. Systematic discrepancies which tend to disappear from averaged data demonstrate some failure in the assumptions underlying the alveolar air equation.

4. Existing information which might throw light upon the sources of failure of the equation is briefly reviewed. The review focuses attention upon the need for more refined techniques in the study of alveolar gases, and particularly in the investigation of practical procedures - such as intermittent pressure breathing - which probably involve radical changes in the conditions under which pulmonary gas exchange takes place.

NATIONAL RESEARCH COUNCIL, DIVISION OF MEDICAL SCIENCES
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COMMITTEE ON MEDICAL RESEARCH
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RESTRICTED

ALVEOLAR RESPIRATORY QUOTIENTS: AN EXPERIMENTAL STUDY OF THE DIFFERENCE BETWEEN TRUE AND ALVEOLAR RESPIRATORY QUOTIENTS, WITH A DISCUSSION OF THE ASSUMPTIONS INVOLVED IN THE CALCULATION OF ALVEOLAR RESPIRATORY QUOTIENTS AND A BRIEF REVIEW OF EXPERIMENTAL EVIDENCE RELATING TO THESE ASSUMPTIONS.

From the Mayo Aero Medical Unit, Rochester, Minnesota by J. B. Bateman and Walter M. Boothby.

1. Introduction.

Through the publication of the recent "Handbook of Respiratory Data in Aviation" wide currency has been given to the idea that changes in the partial pressure of oxygen in the alveoli resulting solely from changes in the fraction of inert gas in the inspired gas mixutre, the other pertinent quantities being kept constnat, can be calculated with the aid of a single additional variable, the metabolic respiratory quotient, Q"'. It is the purpose of the present paper to record new experimental data concerning the validity of this calculation, to examine the assumptions underlying the practical application of the equation involved, and finally to review briefly existing evidence concerning several questions that arise from our statement of the premises. It will be suggested that, althoug these experiments may not greatly affect specifications based upon the calculations presented in the "Handbook", they are not without a certain practical bearing upon the physiology of flight at extreme altitudes.

2. Nomenclature.

Nomenclature slightly simplified from Bateman (1943):

P = barometric pressure

$\bar{P} = P - 47$

pO, pC, pN = partial pressures of oxygen, carbon dioxide and nitrogen in dry inspired gas at pressure P.

The same symbols with one prime (e.g. pO') refer to the partial pressures in the moist inspired gas mixture at body temperature (37° C) ("tracheal" gas).

Two primes refer to "alveolar" partial pressures (thus: pC"), three to moist mixed expired air at body temperature (pN"'), and four to dry expired gas at pressure P.

fO, fC, fN are the corresponding fractions of oxygen, carbon dioxide and nitrogen, related to the partial pressures as follows:

$$fO = pO/P$$

$$fN = pN/P = fN' = pN'/\bar{P}$$

$$fC" = pC"/\bar{P} \quad \text{etc.}$$

3. The alveolar air equation.

The assumptions underlying the alveolar air equation used in the "Handbook" become obvious if the equation is written in symmetrical form as follows:

$$\frac{1}{fN''''}\,(fO'''' + fC''''/Q) = \frac{1}{fN}\,(fO + fC/Q) = \frac{1}{fN''}\,(fO'' + fC''/Q)$$

The left hand equation is the fundamental relation between the composition of inspired and of expired air, and its well-founded derivation need not be repeated here. The right hand equation represents the extension of that on the left to any fraction whatsoever of the expired air. For a given value of Q it is clear that it can apply to any gas that, when mixed with a suitable proportion of fresh inspired gas, will give a mixture identical in composition with the total expired gas. It will not apply, conversely, to any mixture that does not satisfy this condition. This restriction thus limits the validity of the equation to portions of the inspired gas which have exchanged oxygen for carbon dioxide in the proportion 1/Q and have then undergone, to a greater or lesser extent, mechanical admixture with unmodified inspired air. The limitation is important for several reasons. In the first place, it requires gas exchange in the lungs to occur, at each instant throughout the whole respiratory cycle, in more or less strict accordance with the metabolic respiratory quotient Q. This is in sharp contrast to the original equation, which makes allowance for any variations in the relative rates of transfer of oxygen and carbon dioxide that may occur during the respiratory cycle and demands only that a constant overall value of Q be established by the final composition of the total expired air. In the second place, it is necessary that modification of the alveolar gas during its removal from the lung shall occur solely by mechanical admixture and not, to any considerable extent, by diffusion. It is not difficult to imagine that those conditions could be violated very readily if, for example, uptake of oxygen in the lung is much slower and anatomically more circumscribed than loss of carbon dioxide; or if the ratio of blood flow to ventilation should be significantly different in different parts of the lung or should vary significantly during the respiratory cycle.

These premises have not to our knowledge been clearly stated, although they have doubtless been apparent to the several workers who have presented derivations of "alveolar air" equations; nor have they been subjected to any careful experimental scrutiny. A clear vindication would be provided by agreement between values of the respiratory quotient calculated from analyses of total expired air, on the one hand, and from various fractions of so-called "alveolar air", on the other, by means of the two parts of equation (1). Dr. Brink has verbally assured us that the approximate agreement between average respiratory quotients as given in metabolism tables, and as calculated from Boothby's numerous analyses of alveolar air provided the justification for the semi-official adoption of an alveolar air equation for the purposes of aviation physiology. Such approximate agreement of averages for different groups of test subjects is not altogether satisfactory, and indeed, in view of Haldane's statement (Haldane and Priestley 1935, p. 39) that "the true respiratory quotient is about a sixth higher than the alveolar respiratory quotient", is rather unexpected. It seemed desirable, therefore, to put the matter to direct test by determining to what extent changes in respiratory quotient, induced by eating suitable food, and measured by the standard methods of the metabolism laboratory, would be reflected in the composition of the alveolar air as determined by the Haldane-Priestley technique. The experimental part of this paper deals with the results of such experiments.

It should be added that a satisfactory demonstration of the value of equation (1) would not carry with it any implication concerning the gas pressures which actually determine the composition of arterial blood. The generality of the equation is in this

respect its weakness, although in such applications as are propounded in the "Handbook" this is immaterial, since the calculations have reference to the particular mixture of "alveolar" gases that is obtained by a particular technique of collection. It is reasonable to assume that such a mixture will stand in a constant relationship to the "true" alveolar air, but it is not necessary for the two to be identical. This very elementary fact should be kept in mind, because it is always possible that under special conditions of collection of alveolar air - in pressure breathing, for example - the constant relationship may be lost, and the significance of such alveolar analyses may then require reconsideration.

4. Experimental comparison of respiratory quotients.

The experiments consisted of a series of collections of expired air, each being followed immediately by alveolar sampling by the Haldane-Priestley method. The first two determinations were made with the subject in the basal state. The subject then consumed as much boiled rice as possible, and the collection of samples was resumed after an interval of twenty minutes. Two experiments were performed on each of four resting subjects, one at ground level (1,000 feet) and one in the decompression chamber at a simulated altitude of 12,000 feet, breathing air. The following time table illustrates the procedure in a typical experiment:

0 minutes	subject seated quitely in decompression chamber
20-28 minutes	collection of expired air
28 minutes	collection of alveolar air
33 minutes	collection of alveolar air
34-36 minutes	decompress to 12,000 feet simulated altitude
46-54 minutes	collection of expired air
54 minutes	collection of alveolar air
59 minutes	collection of alveolar air
60-66 minutes	rice with sugar and milk being eaten
86-94 minutes	collection of expired air
94 minutes	collection of alveolar air
97-104 minutes	collection of expired air
104 minutes	collection of alveolar air
126-133 minutes	collection of expired air
133 minutes	collection of alveolar air
134 minutes	return to atmospheric pressure

The results are presented in Tables 1 and 2, from which it is apparent that at ground level, over a range of respiratory quotients, Q"', of 0.704 to 0.930, the value Q" calculated from the composition of alveolar air is on the average 0.0155, or roughly 2 per cent, less than the true value, Q"'. At a simulated altitude of 12,000 feet, with Q"' ranging from 0.782 to 0.953, the average difference is 0.0236, or about 3 per cent, in the same sense. Thus stated, the results throw a very favorable light upon the use of the equation (1) and the metabolic respiratory quotient in calculations of the composition of alveolar air. The small average differences, although in the same direction, appear to discredit the discrepancy of 17 per cent noted by Haldane. Closer inspection shows, however, that the low average difference tends to mask the consistent occurence of larger discrepancies in individuals; thus the average value of Q"' - Q" for the one male subject, MC, is + 0.092 at ground level and +0.075 at 12,000 feet, while for the subject, HC, the corresponding mean values are -0.019 and -0.064. These idiosyncracies and their obliteration by the pooling of data for several individuals are also illustrated in Fig. 1, in which Q" is plotted against Q"'. For comparison, Haldane's data (Haldane and Priestley, 1935, p. 39) are also plotted in Fig. 1.

Aside from these individual differences the points that, when averaged, give such close agreement between Q"' and Q" are rather widely scattered. This is obvious from inspection of Tables 1 and 2 and can also be seen in Fig. 2 and Fig. 3, where Q"' and Q" are plotted against time. Although these diagrams show the general trend toward parallel changes in the two quotients, they also show that the uncertainty of measurement is so great that even quite considerable changes in Q"' may be accompanied by opposing changes in Q". Because the chief present interest in the use of equation (1) lies in the calculation of alveolar partial pressures, it is instructive to express this scatter of experimental points quantitatively by comparing the changes in the experimental alveolar partial pressures, pO" and pC", with these calculated from the accompanying changes in Q"'. This procedure has the advantage that of all the measurements made, Q"' is the least subject to error, so that a consistent discrepancy between calculated and observed values of pO" and pC" would serve to throw doubt upon the assumptions underlying the "alveolar" part of equation (1), while random discrepancies would give a measure of the variability of alveolar samples collected by the Haldane-Priestley technique.

For the purposes of our comparison, equation (1) may be used in the following equivalent forms, in which pC is assumed to be zero:

$$pO'' = pO' (1 - pC''/\bar{P}) - (1 - pO'/\bar{P}).pC''/Q \qquad (2)$$

$$pC'' = Q\bar{P} (pO' - pO'') / (Q.pO' + \bar{P} - pO') \qquad (3)$$

The changes in alveolar partial pressures resulting from changes in Q can then be calculated for two extreme cases:

(a) Suppose the change to occur wholly by change in the alveolar oxygen pressure, the ventilation rate being adjusted to keep the carbon dioxide pressure constant, then

$$\partial(pO'')/\partial Q = (1 - pO'/\bar{P}).pC''/Q^2 \qquad (4)$$

(b) Suppose the alveolar carbon dioxide pressure to be affected by the change of Q while the oxygen remains constant; then

$$\frac{\partial(pC'')}{\partial Q} = \frac{\bar{P} (pO' - pO'').(\bar{P} - pO')}{\left[\bar{P} - pO' (1 - Q)\right]^2} \qquad (5)$$

These two extreme cases are illustrated numerically in Fig. 4, in which the ordinate of any point on the appropriate curve represents the increase in alveolar oxygen or carbon dioxide pressure that should accompany an increase of respiratory quotient by 0.1 unit when Q has a mean value given by the abscissa.

The curves are approximate only, and are applicable to the condition of subjects breathing air at altitudes of 0 to 12,000 feet. The fact that the oxygen and carbon dioxide curves do not intersect precisely when Q is unity, as they should according to equations (1), (4) and (5), is due to the fact that the values of pO" and pC" used in the calculation, derived from Boothby's data (reference (1), Chart A-1), are not mutually compatible with equation (1) for all values of Q. The error involved is however not significant for present purposes.

Using Fig. 4, we have calculated for all experiments the changes in alveolar oxygen or carbon dioxide that would be expected according to the change in Q"' which occurred from one set of measurements to the next. The adjustment does not in general occur by a change only in pC" and pO" but by a change in each of these quantities; the sum of the changes in pC" and pO" should however lie somewhere within the range calculated by equations (4) and (5) for the two gases separately. This forms the basis for the

comparison given in Tables 3 and 4 and in Fig. 5; the final column in the tables gives the differences between the observed change, ($\Delta pC'' + \Delta pO''$), and the mean of the changes calculated for oxygen and carbon dioxide separately.

As Fig. 5 illustrates clearly, the uncertainty of measurement is such that in the majority of cases the alveolar partial pressures decrease when an increase would be expected, and vice versa. Expressed numerically, the average discrepancy, regardless of sign, between the observed and calculated alveolar pressures is 3.35 mm. for subjects at ground level (2.59 mm. if the one obviously discordant measurement is omitted), and 2.67 mm. at 12,000 feet simulated altitude. The observed change has a strong tendency to be less than that anticipated; on the average, 2.14 mm. less (1.29 mm. omitting the discordant figure) at ground level and 1.88 mm. less at 12,000 feet. The first pair of figures, 2.59 and 2.67 mm., represents a somewhat smaller scatter than that found in Boothby's 186 observations on a considerable number of subjects at ground level, as would indeed be expected of data obtained by repeated measurements on a small number of individuals.

The second pair, 1.29 and 1.88 mm., are sufficiently large in comparison with the first to carry a strong suggestion of a systematic tendency for the composition of the alveolar air to change less than would be expected in response to changes in respiratory quotient; the magnitude of the effect is however so close to that of the random error of sampling of the Haldane-Priestley method that further work would be necessary to establish it with certainty.

5. Discussion.

The close agreement between average respiratory quotients obtained from total expired air and from alveolar air must be regarded as a vindication of the use of equation (1) in drawing up average requirements for maintenance of alveolar partial pressures within the physiologically permissible range under conditions not too far removed from normal. The consistently low values of the alveolar respiratory quotient reported by Haldane have not been verified in our four subjects taken together but have been observed in one subject, while another subject exhibits the reverse tendency for the alveolar quotient to be too high. Such individual differences point to some lack of uniformity in the character of the alveolar air collected from different persons by the Haldane-Priestley technique, and therefore to some failure, highly variable in degree from person to person, of the assumptions underlying equation (1). The tendency for changes in the composition of Haldane-Priestley alveolar samples to be less than those predicted in response to comparatively large changes in respiratory quotient, with their concomitant changes in ventilation rate and oxygen consumption (cf. Fig. 2 and 3), points to the same conclusion, and it is of interest in this connection to consider existing data on the nature of the changes in alveolar air during the respiratory cycle and to review the ideas which have been advanced by way of explanation. It should be mentioned in passing that although few direct comparisons of alveolar and true respiratory quotients are to be found in the literature, extensive data on the apparent magnitude of the respiratory dead space calculated by Bohr's formula testify to the fact that the two quotients are rarely in perfect agreement, since the dead space calculated from carbon dioxide pressure is systematically smaller than that from oxygen pressures for persons breathing air. It is evident that such a discrepancy implies a difference between Q'' and Q''_1. From equation (1) it follows that if

$$Q'' = Q''_1$$

$$\frac{pC''}{pO' (1 - pC''/\bar{P}) - pO''} = \frac{pC''_1}{pO' (1 - pC''_1/\bar{P}) - pO''_1} \qquad (6)$$

On the other hand, the calculation of dead space is done with the equations

$$V - D_c = V.pC"'/pC" \qquad (7)$$

$$V - D_O = V.(pO' - pO"')/(pO' - pO") \qquad (8)$$

(V = total volume expired, D = dead space),
so that if $D_c = D_O$

$$\frac{pC"}{pO' - pO"} = \frac{pC"'}{pO' - pO"'} \qquad (9)$$

and it can be seen by inspection that equation (9) represents a necessary condition for the equality of Q" and Q"' expressed by equation (6).

Evidence concerning the origin of what we may call diffusion processes in determining the composition of Haldane-Priestley samples, and of implied variations in apparent respiratory quotient, is derived almost exclusively from the results of experiments in which two or more samples of alveolar air are collected during a single expiration. The experiments may involve either the normal alveolar air or the distribution of a foreign gas inhaled prior to the measured expiration. Despite considerable disagreement in points of detail, the information gained is fairly definite in outline, although still ambiguous as to implied interpretation.

The simplest conditions are of course provided by the use of an inert foreign gas which plays no part in respiratory exchange. The early experiments of Siebeck (1910), which were made without fractionation of the expired air, appeared to show an equal distribution of inspired hydrogen in the entire residual air, although according to Siebeck, Grehant (1864) had already shown that of two alveolar samples taken during expiration the first always contained more hydrogen than the second. This has since been repeatedly confirmed both by fractionation procedures (Krogh and Lindhard, 1913; Roelsen 1934, 1938, 1939) and by use of a hot wire method (Aschoff et al. 1940) for continuous recording of expired hydrogen (Mundt, Schoedel and Schwarz, 1940); the rapid fall of hydrogen concentration during washing out of the dead space air is succeeded by a slow continuous decrease throughout expiration. Sonne (1934) has shown a similar decrease to occur after several deep rapid breaths of hydrogen. These results point conclusively to the imperfections of the lung as a mixing chamber, and because of the high rate of diffusion of hydrogen they must represent a conservative estimate. Qualitatively concordant conclusions have been reached by measurements of the rate at which the nitrogen of the residual air is washed out during breathing of pure oxygen (Engelhardt, 1939, Darling, Cournand, and Richards, 1944)

When we consider changes in the composition of expired alveolar air the situation is greatly complicated by continued respiratory exchange during the period of expiration. Measurements of this kind have significance therefore only if allowance can be made for this circumstance. The simplest assumptions that can be made are that respiratory exchange continues throughout the respiratory cycle at the uniform rate established by ordinary determinations of oxygen uptake and carbon dioxide production, and that the composition of expired alveolar air, as found from a sample collected at a given instant, corresponds exactly to the instantaneous composition of the entire residual air. If these assumptions are valid, the observed rate of decrease of alveolar oxygen should agree with the rate calculated from the average rate of oxygen uptake and the total volume of residual and reserve air at the instant of measurement, and the value of Q" should remain constant, and equal to Q"' , for all samples collected. The results of several such comparisons have been

collected in Table 5, which contains only data referring to the middle range of either normal expirations or of deep ("alveolar") expiration preceeded by normal inspiration, and is confined to subjects at rest. The results listed under Krogh and Lindhard have been recalculated to conform to this manner of presentation. Attention is drawn to the following points:

(1) Normal expiration: the data, representing average values for the smoothest part of a normal expiration, show, for two experiments on one individual, approximate agreement between the observed and calculated gradients; for seven experiments, on the other hand, the average observed gradient is considerably greater than that calculated.

(2) Deep expiration: all data show, in the first stages, a consistently higher average rate of apparent oxygen absorption than that calculated, and a fall of alveolar respiratory quotient at a rate of about 0.02 per second. This behavior is succeeded, however, by a region in which, if we leave out of consideration the single experiment of Krogh and Lindhard, the apparent rate of oxygen absorption becomes considerably less than calculated, and may even change in sign, indicating a terminal rise in pO" and fall in pC" (see also Mackay 1940). This is accompanied by a relative constancy, or a slight increase, of Q". The effect appears to be fairly well established, and the wide personal variations recorded would seem to reduce the significance of the single aberrant result obtained from Krogh and Lindard's data.

These data show clearly that the processes underlying the changes in composition of expired alveolar air are somewhat complex. Interpretations vary. Krogh and Lindard, in a somewhat neglected paper, assumed that the apparent rates of oxygen consumption and carbon dioxide production calculated from the changes in alveolar partial pressures were the true instantaneous rates, and that the former values were proportional to the pulmonary blood flow, which was thus shown to be subject to enormous respiratory variations, the pattern of variation being totally different for different types of breathing. On the other hand, Krogh and Lindhard (1917) attributed their results with hydrogen, referred to above, to imperfect mixing in the alveolar sacs, which was supposed to occur chiefly by diffusion and to take an appreciable time. The existence of such gradients, which would surely introduce inconsistencies into Krogh and Lindhard's calculations of pulmonary blood flow, is however doubtful. Mundt, Schoedel and Schwarz (1940) found that a pause between inspiration and expiration had no apparent equalizing effect on the hydrogen distribution; furthermore, modern views as to the mechanism of ventilation by simultaneous increase in length and cross section of alveolar ducts and air sacs, as well as of the larger air passages (cf. Macklin, 1929), would seem to make it probable that regions of imperfect mixing, within a given lobule, would be confined to the layer of stagnant gas in the alveolar depressions, and even these are presumed to become shallower as a result of distention of the air sac during inspiration. If the air sacs be thus regarded as perfect mixing chambers, we must seek to explain manifest irregularities as a result of differences in the ventilation of morphologically distinct regions of the lung. In accepting such a view, which has been particularly strongly urged by Sonne (1934, 1936, 1937, 1940; Sonne and Nielsen, 1932; Nielsen and Sonne, 1932 a, b) and Roelsen (1934, 1938, 1939), we also admit that Krogh and Lindhard's deductions concerning pulmonary circulation must be considerably in error. Sonne and his collaborators attempt to explain the excessively rapid fall in pO" and the rise in pC" as the result of the gradual admixture of air from relatively hyperventilated regions, which is expelled in the earliest stages of expiration, with air from poorly ventilated parts. Since this process

is accompanied by a fall in alveolar respiratory quotient, it is clear that the ventilation and the blood flow in different regions of the lung are not so precisely matched as to give the same relative rates of transfer of oxygen and carbon dioxide; the relationship varies indeed to such an extent that terminal samples may even show a rise in $p\mathcal{Q}''$ and a rise in Q''. This cannot be explained on Krogh and Lindhard's assumptions, and unless due to technical error can only mean that the terminal sample comes from a region which is both poorly ventilated and poorly perfused with blood (Sonne et al).

It is our opinion that the probability, thus established, of regions of unequal ventilation and of unequal perfusion constitutes a modification of Krogh and Lindhard's view rather than a refutation of it. The existence of local differences in blood flow - which have also been directly observed by Wearn and his collaborators (1926, 1934) - does not preclude respiratory changes in average blood flow; these can indeed be inferred from a whole series of phenomena. Much of the immediate value of Krogh and Lindhard's work lies in their emphasis of the changes in alveolar respiratory quotient which inevitably occur during the respiratory cycle as a result of the comparatively steady uptake of oxygen and the gradual decrease in rate of carbon dioxide output as the gradient between the tension of carbon dioxide in the alveoli and in the blood becomes reduced toward the end of expiration. Since this can lead to changes in the instantaneous values of Q'' from about 4.0 to 0.16 during the course of expiration, it is not surprising that certain discrepancies appear in values of Q'' calculated from Haldane-Priestley samples, and that personal idiosyncracy is evident in such data. It is equally clear that uneven ventilation of the lungs would also be expected to lead to discrepancies of the same kind unless there were an extremely fine matching of ventilation with local blood flow. Our own experimental contribution, besides its vindication of the alveolar air formula for limited practical use, has forced our attention upon the inadequacies of the Haldane-Priestley method as a weapon for the further detailed study of gas exchange in the lungs. Having reviewed briefly the available data elucidating some of the factors which are ignored in the Haldane-Priestley technique, we wish to emphasize the urgent importance of the application and extension of this knowledge. On the academic side, the question of the equilibrium between alveolar gases and arterial blood cannot otherwise be carried beyond its present rough and ready state, while the practical value of different forms of intermittent pressure breathing can only be assessed with the aid of an intimate knowledge of the effect of such procedures upon the course of gas exchange in the lungs.

References

Aschoff, J., Mundt, E., Schoedel, W. and Schwarz, H. 1940. Pflueg. Arch. ges. Physiol., 244, 87.

Bateman, J. B. 1943. O.S.R.D., Committee on Aviation Medicine, Report No. 222.

Darling, R. C., Cournand, A. and Richards, D. W. 1944. J. Clin. Invest., 23, 55.

Engelhardt, A. 1939. Z. Biol., 99, 596.

Grehant, N. 1864. J. de l'anat. et de la physiol., 1, 523. Cited by Siebeck, 1910.

Grosse-Brockhoff, F. and Schoedel, W. 1937. Unpublished data cited by Schoedel, 1937.

Haldane, J. S. and Priestley, J. G. 1935. Respiration. Yale University Press, New Haven.

Handbook of Respiratory Data in Aviation, O.S.R.D., C.M.R., Washington, D. C., 1944.

Krogh, A. and Lindhard, J. 1913. J. Physiol., 47, 30.

Krogh, A. and Lindhard, J. 1914. Biochem. Z., 59, 260.

Krogh, A. and Lindhard, J. 1917. J. Physiol., 51, 59.

Mundt, E., Schoedel, W. and Schwarz, H. 1940. Pflueg. Arch. ges. Physiol., 244, 99.

Mackay, I. F. S., 1940, J. Physiol., 98, 73.

Macklin, C. C., 1929. Physiol. Rev., 9, 1.

Nielsen, E. and Sonne, C. 1932 a. Z. ges. exp. Med., 85, 46.

Nielsen, E. and Sonne, C. 1932 b. Acta medica Scand., Suppl. 50, 33.

Roelsen, E. 1934. Acta medica Scand., Suppl. 59, 356.

Roelsen, E. 1938. Acta medica Scand., 95, 452.

Roelsen, E. 1939. Acta medica Scand., 98, 141.

Schoedel, W. 1937. Ergebn. Physiol., 39, 450.

Siebeck, R. 1910. Z. Biol., 55, 267.

Sonne, C. and Nielsen, E. 1932. Acta medica Scand., Suppl. 50, 26.

Sonne, C. 1934. Z. ges. exp. Med., 94, 13.

Sonne, C. 1936. Acta medica Scand., 90, 315.

Sonne, C. 1937. Scand. Arch. f. Physiol., 75, 127.

Sonne, C. 1940. Acta medica Scand., 105, 313.

Wearn, J. T., Barr, J. S. and German, W. J. 1926-27. Proc. soc. exp. biol. med., 24, 114.

Wearn, J. T., Ernstene, A. C., Bromer, A. W., Barr, J. S., German, W. J. and Zschiesche, L. J., Am. J. Physiol., 109, 236.

Table 1

EXPERIMENTS AT GROUND LEVEL

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
		Time		V	Expired Air		Alveolar Air				
Date	Subj.	(min.)	P	L/min.	pO_2'''	pCO_2'''	pO_2''	pCO_2''	Q'''	Q''	$Q''' - Q''$
12/22/42	HC(f)	52-41	740.4	6.32	121.6	19.0	106.9	32.5	0.759	0.809	-0.050
		37-25		6.55	121.2	18.2	106.8	33.1	0.704	0.823	-0.119
		20-29		8.97	121.8	20.1	95.1	35.8	0.822	0.662	+0.160
		33-40		10.04	125.2	18.8	108.5	33.7	0.918	0.898	+0.020
		81-91		8.36	122.6	19.4	109.0	34.0	0.820	0.925	-0.105
1/13/43	HC(f)		743.2	7.13	123.2	18.1	107.6	30.8	0.757	0.761	-0.004
				--	--	--	105.3	30.9	--	0.712	--
12/22/42	LC(f)	47-37	740.4	7.08	117.7	21.8	102.8	34.3	0.742	0.762	-0.020
		33-22		7.88	119.8	21.0	103.1	34.0	0.763	0.764	+0.019
		20-30		8.74	119.5	22.5	106.2	35.7	0.838	0.890	-0.052
		35-45		9.55	121.4	21.4	100.3	36.5	0.864	0.769	+0.095
		84-93		8.90	119.3	22.5	103.5	36.5	0.830	0.844	-0.014
1/4/43	LC(f)		733.3	7.84	119.6	21.5	105.4	33.1	0.854	0.829	+0.025
				--	--	--	104.6	31.1	--	0.748	--
12/28/42	RS(f)	47-35	738.6	7.77	119.3	22.4	111.2	31.4	0.840	0.911	-0.071
		29-19		7.78	117.8	22.9	107.8	32.6	0.804	0.847	-0.043
		22-31		9.40	119.6	23.5	111.5	31.7	0.908	0.933	-0.025
		37-45		9.50	120.3	23.3	110.9	33.5	0.930	0.974	-0.044
		84		9.20	119.0	23.7	--	--	0.888	--	--
1/12/43	RS(f)	--	742.7	6.89	121.2	22.5	108.0	33.9	0.889	0.871	+0.018
		--		--	--	--	102.8	35.6	--	0.790	--
12/28/42	MC(m)	37-29	738.6	11.45	125.2	16.3	99.5	34.9	0.784	0.721	+0.063
		23-16		12.27	125.9	16.3	99.8	35.8	0.814	0.750	+0.064
		24-30		14.50	125.1	17.8	100.4	36.2	0.867	0.772	+0.095
		36-43		13.51	124.8	18.9	101.7	35.7	0.922	0.786	+0.136
		83-89		13.34	124.1	18.8	99.9	36.5	0.873	0.770	+0.103
12/31/42	MC(m)		733.9	10.93	122.2	18.5	98.0	34.8	0.814	0.708	+0.106
				--	--	--	98.6	34.2	--	0.705	--
										Mean	+0.0155

Table 1 Cont'd.

Explanation: Column (2): f = female
m = male

Column (3): Times are reckoned from time at which subject finished eating rice. Negative sign is omitted from times preceding rice eating. The second figure in each horizontal pair gives the time of completion of collection of expired air and also the time at which alveolar sample was taken.

Column (5): V = ventilation rate in liters per minute at ambient pressure, body temperature, and saturated with water vapor.

Columns (10) and (11) = respiratory quotients calculated from analyses of expired air (Q'') and of alveolar air (Q'') by equation (1), suitably rearranged.

TABLE 2

Experiments at 12,000 Feet

(1) Date	(2) Subject	(3) Time	(4) P	(5) V	(6) pO''_t	(7) pC''_t	(8) pO''	(9) pC''	(10) Q''_t	(11) Q''	(12) $Q''_t - Q''$
13 Jan.	HC (f)	22-12	481.6	7.80	70.5	16.9	59.8	28.1	0.782	0.872	-0.090
		-7		—	—	—	52.6	30.6	—	0.750	—
		20-28		10.85	71.2	18.3	62.1	28.9	0.897	0.991	-0.094
		30-38		11.05	71.6	18.3	62.1	27.7	0.916	0.943	-0.027
		60-67		11.65	72.1	17.6	62.4	28.1	0.912	0.977	-0.065
4 Jan.	LC (f)	20-12	477.9	8.63	68.0	19.9	54.0	30.6	0.859	0.806	+0.053
		-7		—	—	—	54.1	28.7	—	0.750	—
		20-28		9.97	67.4	19.2	55.9	29.9	0.795	0.834	-0.039
		31-38		10.67	68.5	19.2	53.8	31.0	0.850	0.812	+0.038
		60-67		11.01	68.5	20.0	49.1	33.4	0.892	0.770	+0.122
12 Jan.	RS (f)	21-13	477.7	7.95	66.5	21.3	53.2	32.6	0.871	0.849	+0.022
		-8		—	—	—	49.6	32.1	—	0.746	—
		21-28		9.93	66.4	21.7	56.0	31.7	0.865	0.889	-0.024
		32-38		10.13	68.0	21.9	53.5	33.3	0.953	0.869	+0.084
		60-68		9.49	67.2	22.2	54.5	32.7	0.924	0.878	+0.046
31 Dec.	MC (m)	34-28	481.6	12.46	71.4	17.6	55.4	28.1	0.866	0.745	+0.121
		23-17		12.20	70.7	17.9	53.5	30.7	0.843	0.777	+0.066
		20-26		14.64	71.2	18.0	51.0	32.4	0.890	0.774	+0.016
		32-37		16.27	71.9	16.8	51.8	31.6	0.866	0.768	+0.092
		76-81		17.00	73.4	16.0	54.6	30.6	0.882	0.802	+0.080
										Mean	+0.0236

Explanation: See Table 1

TABLE 3.

Comparison of Observed and Calculated Changes of Alveolar Partial Pressures

Experiments at Ground Level

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
								Observed	Calculated		from Q"'	Discrepancy
Date	Subject	Q"'	ΔQ"'	pC"	ΔpC"	pO"	ΔpO"	ΔpC"+ ΔpC"	ΔpC"	pO"	Average	(12)—(13)
22 Dec.	HC	0.759		32.5		106.9						
			-0.055		+0.6		- 0.1	+ 0.5	-2.1	-2.9	-2.5	- 3.0
		0.704		33.1		106.8						
			+0.118		+2.7		-11.7	- 9.0	+4.4	+5.7	+5.4	-14.0
		0.822		35.8		95.1						
			+0.096		-2.1		+13.4	+11.3	+3.4	+3.5	+3.5	+ 7.8
		0.918		33.7		108.5						
			-0.098		+0.3		+ 0.5	+ 0.8	-3.4	-3.6	-3.5	- 4.3
		0.820		34.0		109.0						
22 Dec.	LC	0.742		34.3		102.8						
			+0.041		-0.3		+0.3	0	+1.5	+2.0	+1.8	-1.8
		0.783		34.0		103.1						
			+0.055		+1.7		-3.1	- 1.4	+2.0	+2.3	+2.2	-3.6
		0.838		35.7		106.2						
			+0.026		+0.8		-5.9	-5.1	+0.9	+1.0	+1.0	-6.1
		0.864		36.5		100.3						
			-0.034		0		+3.2	+3.2	-1.2	-1.3	-1.3	-4.5
		0.830		36.5		103.5						
28 Dec.	RS	0.840		31.4		111.2						
			-0.036		+1.2		-3.4	-2.2	-1.3	-1.5	-1.4	+0.8
		0.804		32.6		107.8						
			+0.104		-0.9		+3.7	+2.8	+3.7	+4.1	+3.9	-1.1
		0.908		31.7		111.5						
			+0.022		+1.8		-0.6	+1.2	+0.8	+0.7	+0.7	+0.5
		0.930		33.5		110.9						
28 Dec.	MC	0.784		34.9		99.5						
			+0.030		+0.9		+0.3	+1.2	+1.1	+1.3	+1.2	0
		0.814		35.8		99.8						
			+0.053		+0.4		+0.6	+1.0	+1.9	+2.1	+2.0	-1.0
		0.867		36.2		100.4						
			+0.055		-0.5		+1.3	+0.8	+1.9	+1.9	+1.9	-1.1
		0.922		35.7		101.7						
			-0.049		+0.8		-1.8	-1.0	-1.7	-1.7	-1.7	-0.7
		0.873		36.5		99.9						
											Means:	3.35 mm

Table 3 - Cont'd.

Columns (10) and (11) represent the possible changes in pC" at constant pO", or in pO" at constant pC", corresponding to the changes in Q" recorded in column (4), according to Fig. 3.

In column (13) the average of these values is compared, by subtraction, with the sum of the observed changes in pO" and pC". Negative sign before a value in column (13) indicates that the observed change was less than that calculated, including those cases in which the observed and calculated values changed in opposite directions.

TABLE 4

Comparison of Observed and Calculated Changes of Alveolar Partial Pressures

Experiments at 12,000 feet

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
Date	Subject	Q":	ΔQ":	pC"	ΔpC"	pO"	ΔpO"	Observed ΔpC"+ΔpO"	Calculated from Q": ΔpC"	ΔpO"	Average	Discrepancy (12)–(13)
13 Jan.	HC	0.782		30.6		52.6						
			+0.115		-1.7		+9.5	+7.8	+4.1	+4.5	+4.3	+3.5
		0.897		28.9		62.1						
			+0.019		-1.2		0	-1.2	+0.7	+0.7	+0.7	-1.9
		0.916		27.7		62.1						
			-0.004		+0.4		+0.3	+0.7	-0.1	-0.1	-0.1	-0.8
		0.912		28.1		62.4						
4 Jan.	LC	0.859		28.7		54.1						
			-0.064		+1.2		+1.8	+3.0	-2.3	-2.6	-2.5	-5.5
		0.795		29.9		55.9						
			+0.055		+1.1		-2.1	-1.0	+2.0	+2.3	+2.2	-3.2
		0.850	+0.042	31.0	+2.4	53.8	-4.7	-2.3	+1.5	+1.6	+1.6	-3.9
		0.892		33.4		49.1						
12 Jan.	RS	0.871		32.1		49.6						
			-0.006		-0.4		+5.4	+5.0	-0.2	-0.2	-0.2	-5.2
		0.865		31.7		56.0						
			+0.088		+1.6		-2.5	-0.9	+3.1	+3.1	+3.1	-4.0
		0.953		33.3		53.5						
			-0.029		-0.6		-1.0	-1.6	-1.0	-0.9	-1.0	+0.6
		0.924		32.7		54.5						
31 Dec.	MC	0.866		28.1		55.4						
			-0.023		+2.6		-1.9	+0.7	-0.8	-0.8	-0.8	-1.5
		0.843		30.7		53.5						
			+0.047		+1.7		-2.5	-0.8	+1.6	+1.7	+1.7	-2.5
		0.890		32.4		51.0						
			-0.030		-0.8		+0.8	0	-1.0	-1.1	-1.1	-1.1
		0.860		31.6		51.8						
		0.882	+0.022	30.6	-1.0	54.6	+2.8	+1.8	+0.8	+0.8	+0.8	+1.0
											Mean:	2.67
												-1.88

Explanation: See legend to Table 3.

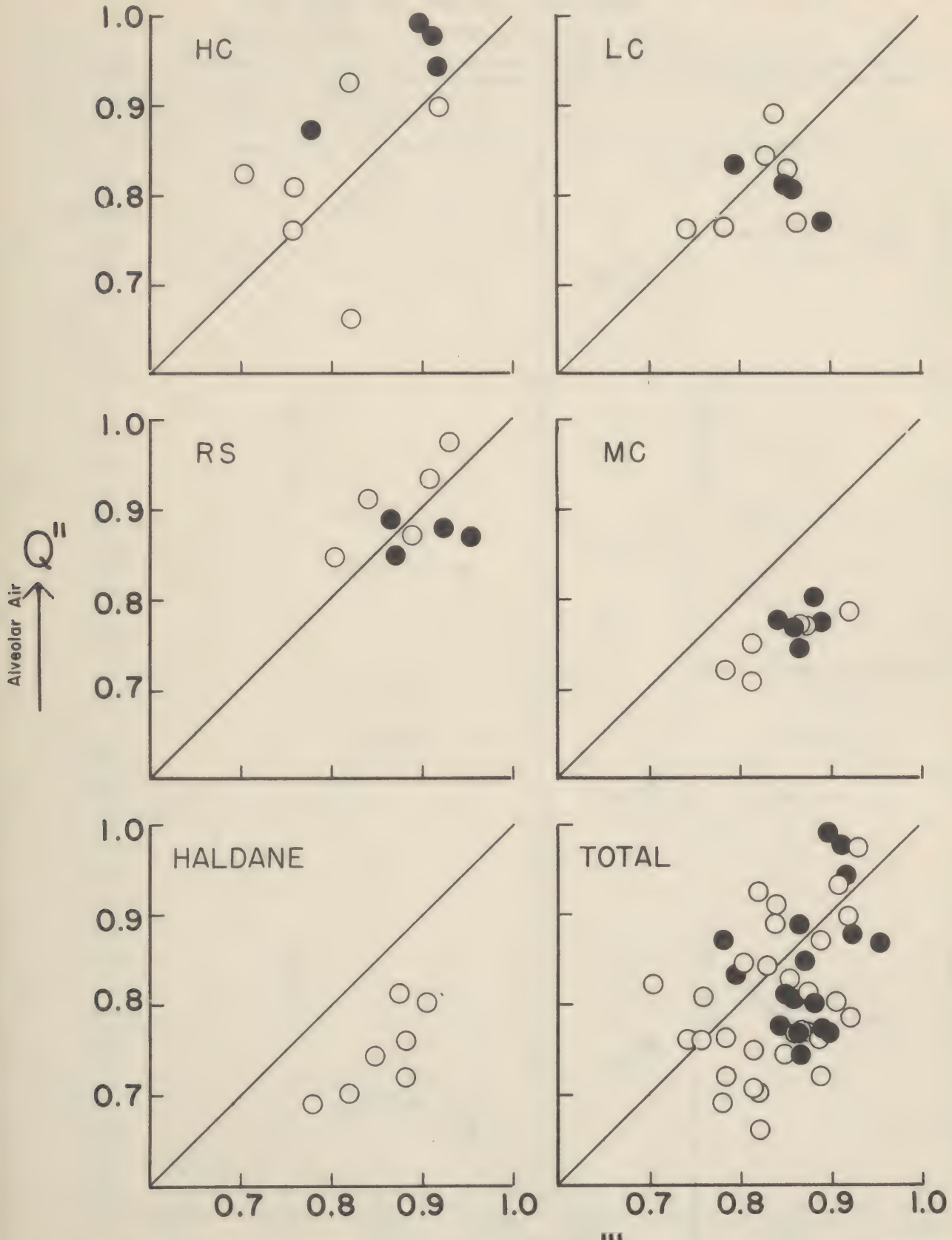
TABLE 5

Rate of Change of Partial Pressure of Oxygen in Alveolar Air During Expiration

Authors	Number of Experiments	Type of Expiration	I			II		
			d(pO")/dt		dQ"/dt	d(pO")/dt		dQ"/dt
			Observed	Calculated		Observed	Calculated	
Krogh and Lindhard, 1914	2	Normal	-0.9	-1.0		—	—	—
Grosse-Brockhoff and Schoedel, 1937	7	Normal	-2.2	-1.5	—	—	—	—
Krogh and Lindhard, 1914	1	Deep	-2.2	-1.1		-3.4	-1.4	
Nielsen and Sonne, 1932 Sonne, 1934	29	Deep	-3.5	-1.4	-0.022	+0.14	-2.1	+0.007
Roelsen, 1939 a	26	Deep	-2.9	-1.3	-0.025	-0.9	-1.7	-0.003

Note: Values of d (pO")/dt are in mm. Hg per second.
Calculated values are obtained from average oxygen consumption and volume of air in lungs, assuming uniform blood flow throughout the respiratory cycle.

COMPARISON OF RESPIRATORY QUOTIENTS CALCULATED FROM ANALYSES OF ALVEOLAR AND TOTAL EXPIRED AIR



Mayo Aero Medical Unit

Chart I– 11a

○ GROUND ● 12,000 FEET

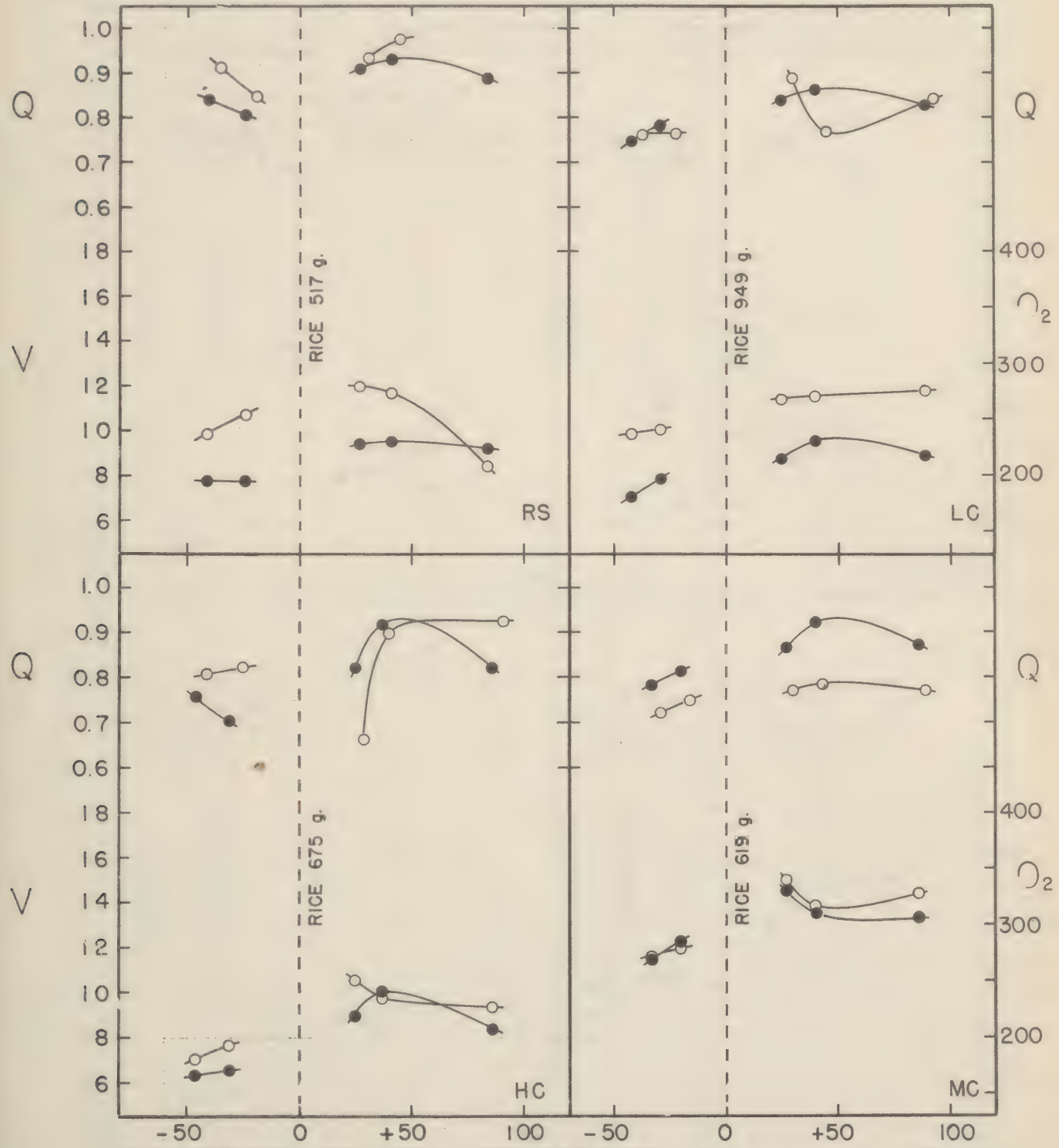
J.B. Bateman and W.M. Boothby
June 1944

Fig. 1

TIME COURSE OF CHANGE OF TRUE RESPIRATORY QUOTIENT AND ALVEOLAR RESPIRATORY QUOTIENT AFTER A MEAL OF RICE

DATA OBTAINED AT GROUND LEVEL (1,000 FEET)

Upper section of each quadrant contains points for true respiratory quotient Q‴ ● and for alveolar respiratory quotient Q″ ○
Lower sections show ventilation rate in liters per minute (atmospheric pressure, 37° C, 47 mm. water vapor), ● and oxygen consumption in c.c. per minute at 760 mm., 0° C, dry.
Abscissa: time in minutes. Zero is time at which meal of rice was finished.



Mayo Aero Medical Unit
Chart I – 11b June 1944

J. B. Bateman
W. M. Boothby

Fig. 2

TIME COURSE OF CHANGE OF TRUE RESPIRATORY QUOTIENT AND ALVEOLAR RESPIRATORY QUOTIENT AFTER A MEAL OF RICE

DATA OBTAINED AT 12,000 FEET SIMULATED ALTITUDE

Upper section of each quadrant contains points for true respiratory quotient, Q‴, and for alveolar respiratory quotient, Q″.
Lower sections show ventilation rate in liters per minute (ambient pressure, 37°C, 47mm. water vapor), and oxygen consumption in cc. per minute at 760 mm., 0° C, dry
Abscissa: Time in minutes. Zero is time at which meal of rice was finished.
Dotted line on left of each qradrant shows point of ascent to 12,000 feet.

Q″ V	Q″ O2
●	○

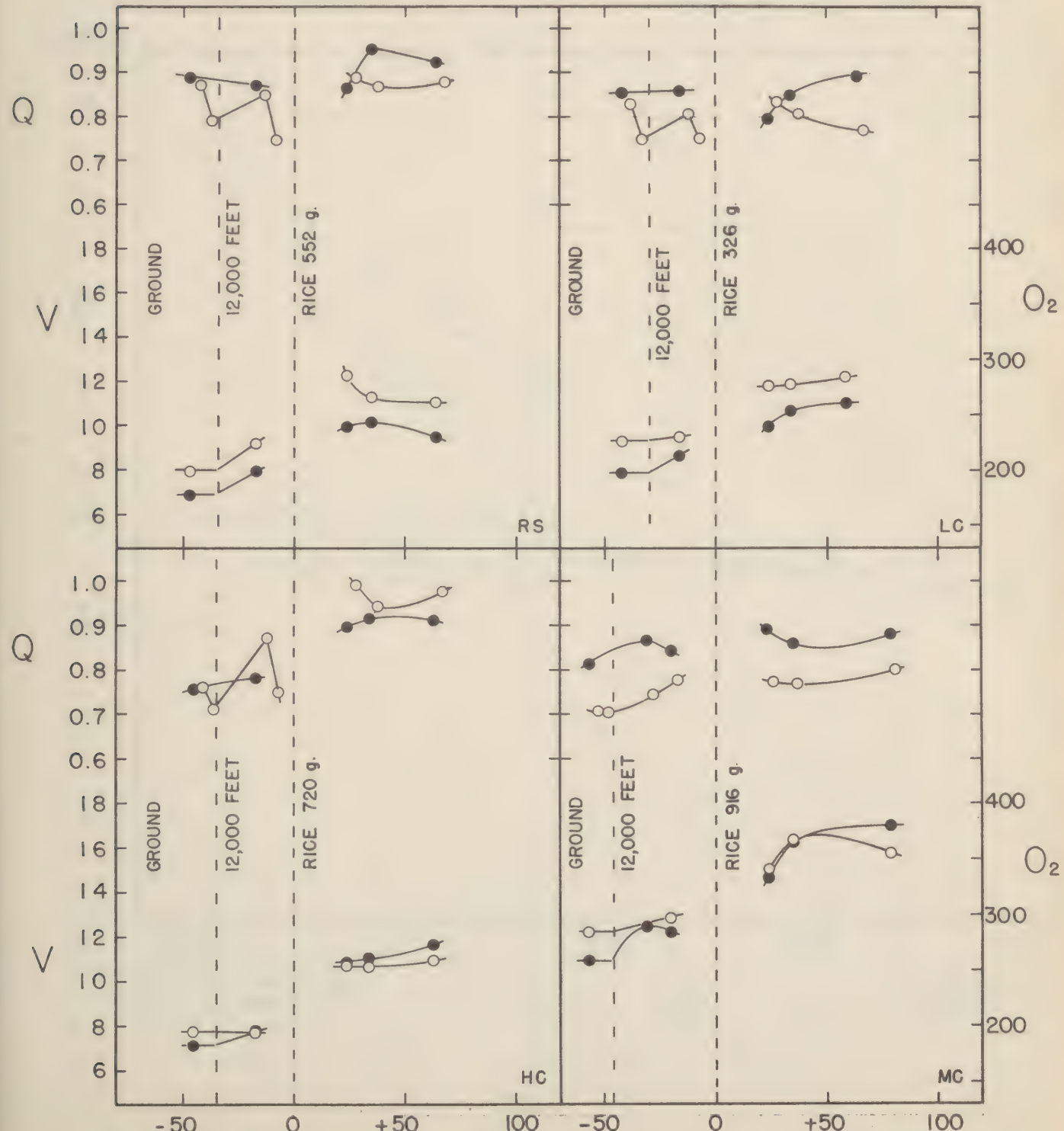


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Chart I-11c June 1944

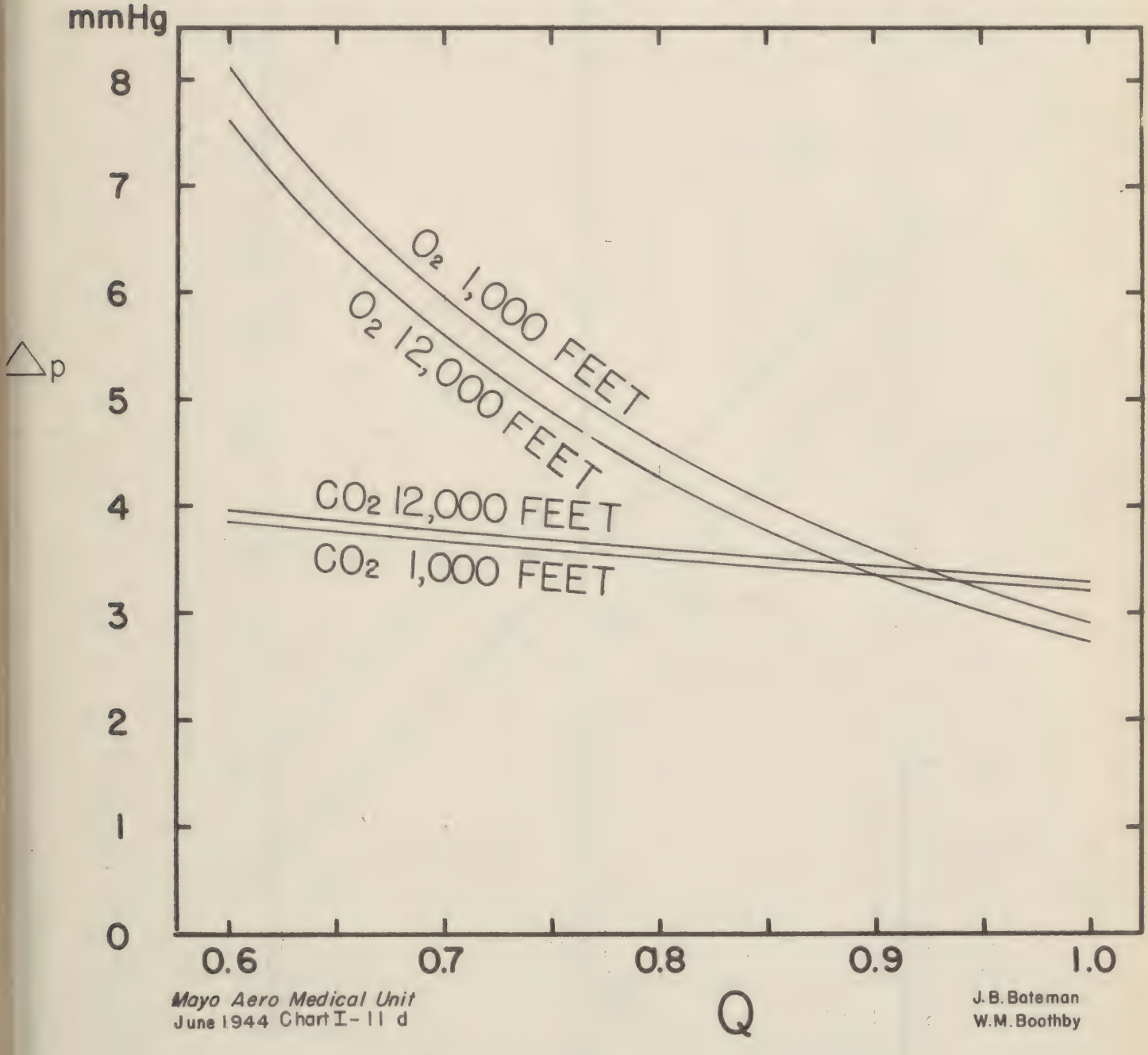
Fig. 3

J.B. Bateman
W.M. Boothby

VARIATION OF ALVEOLAR PARTIAL PRESSURES WITH RESPIRATORY QUOTIENT

O_2 Curves : change in pO'' for 0.1 unit change in Q at constant pC''

CO_2 Curves : change in pC'' for 0.1 unit change in Q at constant pO''



Mayo Aero Medical Unit
June 1944 Chart I-11 d

J. B. Bateman
W. M. Boothby

COMPARISON OF OBSERVED CHANGES IN PARTIAL PRESSURES WITH THOSE CALCULATED FROM CHANGES IN RESPIRATORY QUOTIENT OCCURRING AFTER A MEAL OF RICE

Abscissa: Calculated change, $\triangle pC'' + \triangle pO''$. Ordinate: Measured change, $\triangle pC'' + \triangle pO''$
Units : Millimeters of mercury. O Ground level, 1,000 feet. ● 12,000 feet.
Points representing measured changes smaller than those calculated must all fall within sectors AOB and COD.
The pairs of lines parallel to AOD represent the average discrepancy between calculated and measured values.

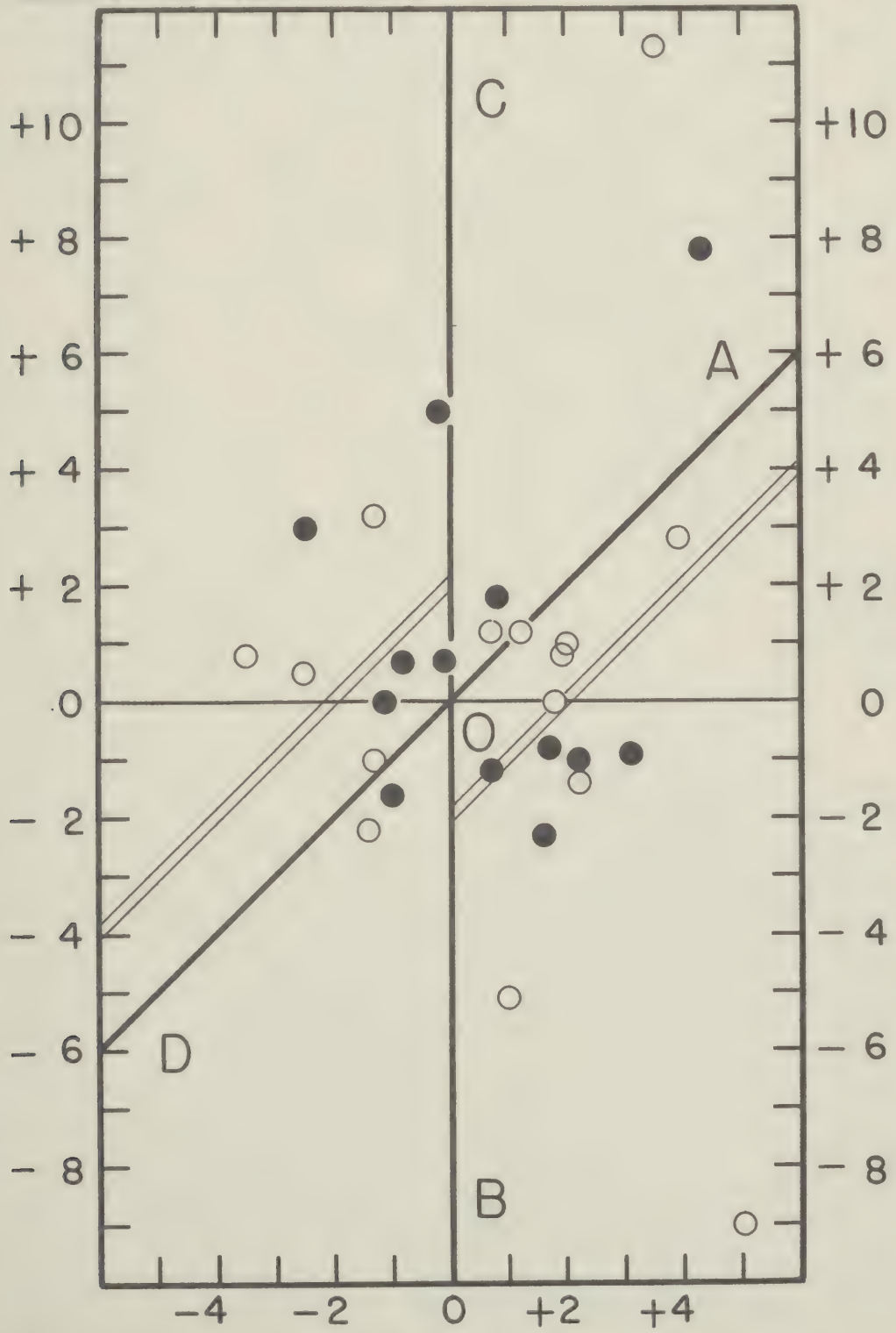


Fig. 5

Mayo Aero Medical Unit
Chart I–11e June 1944

J.B. Bateman
W.M. Boothby

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Office of Scientific Research and Development
COMMITTEE ON AVIATION MEDICINE

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Report No. 360
August 1944

THE EFFECTS OF ALTITUDE ANOXIA ON THE RESPIRATORY PROCESSES.

From the Mayo Aero Medical Unit, Rochester, Minnesota, by H. F. Helmholz, Jr., J. B. Bateman and W. M. Boothby.

SUMMARY

This paper is a summary of some results of analysis of alveolar gas from persons breathing air at simulated altitudes up to 22,000 feet or pure oxygen up to 42,000 feet. The data are amenable to representation in simple diagrams which can be made the basis for discussion of several respiratory phenomena. This graphic approach has the advantage that while an alveolar air equation covers a whole series of physically possible states, the experimental data show which of these are actually met with physiologically. At the same time they can be shown to be in harmony with the more general physical statement.

The presentation given here is used to show in simple terms the slight difference in specifications for oxygen supply systems that arise from the use of different reference points - on the one hand the "tracheal" reference point adopted by the Army and Navy and on the other the "alveolar" reference point advocated by a number of physiologists. The essential part played by the alveolar respiratory quotient in the production of these differences is emphasized.

An analysis of the mechanism of the adaptation to mild anoxia is given with reference to the following points:

1. (a) The distinction between the "steady state" of respiratory exchange which occurs under conditions within the limited range of normal adjustment mechanisms, the "semi-steady state" established as a temporary adjustment to respiratory stresses (such as anoxia) which are outside the permanently allowable range, the "non-steady state" of rapid transition.

   (b) The time needed to establish a new steady state under mildly anoxic conditions. New data are presented in illustration of this point.

2. The probable increases in circulation rate which are necessary at various altitudes in order to prevent undue decrease of venous oxygen pressure. The results of an estimate of relative cardiac output at different altitudes, based upon the alveolar air data, are presented in a new diagram where they are compared directly with the available experimental determinations of cardiac output of anoxic subjects. The discussion which follows is directed toward the use of present knowledge as a pointer for further experimental work.

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In the study of respiration (including circulation) at varying atmospheric pressure, the fundamental changes encountered must necessarily involve differences in the conditions of transfer of gases across the alveolar membrane. In the past years this laboratory has had wide experience with alveolar air analysis, and a presentation of data in a compact form and to serve as some sort of exposition of the implications seems in order. In addition, many gaps in our knowledge can be emphasized by such a recapitulation.

The Haldane-Priestley method for collecting alveolar air samples as used at the Mayo Aero Medical Unit requires collection of the last fraction of a complete, vigorous exhalation started at the normal beginning of exhalation. This fraction is analyzed in a modified Haldane apparatus, by trained technicians. The results are reported as partial pressures in millimeters of mercury calculated from the barometric pressure (less 47 mm. for water vapor) at the time the sample was taken. These samples have been shown, by comparisons with direct (Van Slyke) and indirect (oximeter) methods, to have partial pressures which correspond to those in the blood when the means of many observations are considered (16), (18), (8), (17), (15), (5), (9), (10) and (22). This is the best available evidence that such samples indicate the actual composition of the gas mixture in contact, through the alveolar membrane, with the circulating blood. Discrepancies which have been found at sea level atmospheric pressures between alveolar oxygen pressures and hemoglobin saturations calculated from the oxygen content of arterial blood have been analyzed in a recent paper by Roughton, Darling and Root, who attribute them to experimental error.

"Tracheal" air formulation. The continued study of alveolar air is primarily of interest to the physiologist. From the practical point of view, especially for purposes of designing oxygen equipment, it has been decided by the Army and the Navy to consider only the partial pressures in the "tracheal" air, i.e. the inhaled gas mixture saturated with water vapor at 37° C. Thus, in oxygen regulator design, the specifications call for provision of oxygen-air mixtures which will maintain a given oxygen partial pressure in the "tracheal" air with changing barometric pressure. This has proved to be a satisfactory standard. In no sense is the continued presentation of alveolar air data a suggestion that the latter should be considered in the design of ordinary oxygen equipment.

As Bateman reiterated in Report 222 to the Committee on Aviation Medicine on "Tracheal" versus "Alveolar" Air, the use of the "tracheal" air formulation in calculating equivalent altitudes will on certain theoretical assumptions require the use of slightly more oxygen than that needed if the alveolar air is the reference point, especially at higher altitudes. However, it is well to remember that this amount is insignificant in relation to the variation inherent in any hitherto designed automatic mixing devices in which variation in demand is put upon the oxygen delivery valve. Moreover, different methods of using the alveolar air formulation give discordant estimates of equivalent altitude under conditions involving mild anoxia, especially when the phenomena of acclimatization to high ground elevations are considered. These differences, undoubtedly of scientific interest, would make the picture unnecessarily complicated as a basis for engineering recommendations. It is also known, as Bateman remarks, that the variation between individual alveolar air values forming the basic data is greater than the difference between equivalent altitudes derived by the two methods. These facts all clearly vindicate the official adherence to a "tracheal" air formulation.

Alveolar air formulation. By definition, the tracheal air formulation makes no reference to the gas exchange in the lungs. It therefore fails to describe certain effects arising from the fact that during this process the amount of carbon dioxide received by the alveolar gases is seldom equal to the amount of oxygen removed in a given time. Such effects are implicit in any good formulation of the composition of alveolar air and its dependence upon the alveolar respiratory quotient (4), (10a), (23), (12), (7) but it has sometimes been difficult for those concerned with aviation physiology to visualize the effects implied algebraically in these formulations. Because of their essential role as a basis for the physiology of respiration, repeated attempts have been made to show graphically how experimental data on the alveolar gases conform to the predictions of the formulae. Such data were presented in 1940 by Boothby, Lovelace and Benson for subjects breathing air, oxygen-air mixtures, and pure oxygen at different simulated altitudes up to 40,000 feet. During the next three years, many additional observations were made, and it was shown that other methods of collecting alveolar air gave essentially the same values as that of Haldane and Priestley. All observations on subjects breathing air at simulated altitudes from the ground (1,000 feet) to 20,000 feet were presented on charts submitted to the Committee on Aviation Medicine by Boothby and included in the Handbook (22) published under the auspices of the Subcommittee on Oxygen and Anoxia.

The alveolar air equation in its several equivalent forms represents a relationship which must be valid within the limits of validity of the several assumptions tacitly involved (3) if gas mixtures containing oxygen, carbon dioxide and other inert gases supply the oxygen needed and remove the carbon dioxide produced during any period of bodily function. The assumptions are on the whole justified provided the body is in a steady or semi-steady state - by which we mean for the present only that the respiratory cycle (in which we include the circulating blood) shall maintain its identity over a number of respirations. Any sensible drift will upset the relationships established by the more or less exact repetition of a cycle and will render the equation invalid. Apart from this limitation, the experimental study of the remaining assumptions, implicit in some early observations of J. S. Haldane (13) and others, has been resumed by Bateman and Boothby (3), whose data justify Brink's use of a combustion quotient when using the equation in calculations of average equivalent altitudes for large groups of people. Such a step implies

that the relationships of the equation apply equally to inspired, alveolar, and total expired air, or to any mixture of these. In attempting to give a verbal explanation and to correlate the graphic with the algebraic statements, we shall present a simplified equation relating only to alveolar and carbon-dioxide-free inspired air:

$$\underline{\text{Inspired Air}} \qquad\qquad \underline{\text{Alveolar Air}}$$
$$\frac{1}{\%\ N_2} \times (\%\ O_2) = \frac{1}{\%\ N_2} \times \%\ O_2 + \frac{\%CO_2}{R.Q.} \quad \ldots\ldots\ldots (1)$$

We must also bear in mind that all the partial pressures add up to the atmospheric pressure:

Inspired air pressure = atmospheric air pressure = alveolar air pressure.
$IpN_2 + IpO_2 + 47$ = Barometric pressure = $ApN_2 + ApO_2 + ApCO_2 + 47$ . . . . . (2)
Where I and A represent inspired and alveolar air respectively and pN_2, pO_2 and pCO_2 represent the partial pressure of nitrogen, oxygen and carbon dioxide respectively and 47 mm. the average pressure of water at body temperature of 37° C.

The essential process occurring in the alveoli is the removal of oxygen from the alveolar gas and the simultaneous addition of carbon dioxide. If the body is in a steady state, the ratio of the number of molecules of carbon dioxide produced to the number of molecules of oxygen absorbed in a time covering any whole number of identical respirations will correctly represent the ratio of the rates of turnover of these substances resulting from the oxidative processes of the body. In other words, the alveolar respiratory quotient will be identical with the combustion quotient. When the body is in a semi-steady state, this is not the case, because we have superimposed upon the strictly metabolic exchanges between blood and tissues an abnormal pulmonary exchange of carbon dioxide, usually the consequence of some reflex or voluntary change in the character of the breathing. This abnormality must of course be reflected in the exchange between blood and tissues and tissue fluids, including the production of urine, and must ultimately react in a deleterious manner upon tissue metabolism and the mechanism for the maintenance of a constant internal environment. Strictly speaking, whenever the gas exchange in the lungs is disturbed in such a manner as to introduce a discrepancy between the apparent respiratory quotient and the true combustion quotient, it is impossible for any one breath to be precisely identical with its predecessor; the fact that we can sometimes speak of virtual identity and a "semi-steady state" chiefly arises from the circumstance that the buffering power of the tissues permits a relatively large amount of carbon dioxide to be removed without producing a significant change in pH. Thus it is often possible to establish, and to characterize by means of apparent respiratory quotients, semi-steady states which persist long enough to be of considerable importance in some of the emergency situations encountered in high altitude flying. The transition period between a steady state and a semi-steady state or a new steady state is one of rapid change, often of very brief duration, in which alveolar air analyses are difficult to reproduce and impossible to interpret reliably. During this period of rapid change the subject is in a non-steady state.

It is this potentially variable relationship between the oxygen and carbon dioxide transfer across the alveolar membrane that has caused some confusion in the comparison of the effects of breathing air and oxygen under various conditions met with in aviation. When pure oxygen is being breathed, there is no particular

difficulty. If the number of carbon dioxide molecules produced is smaller than the number of oxygen molecules absorbed, more pure oxygen will move in to maintain the total pressure equal to that of the atmosphere, and it will be impossible to distinguish by means of alveolar gas analyses, between the oxygen which was originally present and that which has moved in to make up for a deficit of carbon dioxide. In other words, we can learn nothing about the alveolar respiratory quotient from measurements of this type. Now when air is being breathed the situation is quite different. In this case a deficit in the total number of oxygen and carbon dioxide molecules (R.Q. less than unity) causes an increase in the fraction of nitrogen present; the air of the atmosphere, acting as a piston, will compress this mixture deficient in molecules as a result of pulmonary exchange, to maintain atmospheric pressure. The result must be an increase in the partial pressure of nitrogen in the alveoli - an increase that will depend upon the respiratory quotient in the manner indicated in equation (1). It is this change in nitrogen pressure that has caused some of the confusion; but to the same phenomenon we owe the possibility of measuring respiratory quotients by analyses of expired air or alveolar air. J.S.Haldane realized this many years ago. The nitrogen acts as an inert indicator, so to speak, of changes in the total number of "active" molecules in the lung. When the respiratory quotient is less than unity, we can detect the fact by an increase in the partial pressure of nitrogen; when, in a semi-steady state, it is greater than unity, the partial pressure of nitrogen decreases, and the alveolar gas contains relatively more oxygen than it did before.

The same effect is responsible for some of the differences between equivalent altitudes calculated according to the "tracheal" and "alveolar" reference points. The increase in nitrogen pressure depends upon the fraction of nitrogen in the inspired air; the more oxygen and the less nitrogen there is, the less significant is the effect of the respiratory quotient in increasing or decreasing the partial pressure of oxygen, and the closer the parallelism between the "tracheal" and the alveolar oxygen pressures. Another consequence is that the temporary establishment of a higher alveolar oxygen pressure by hyperventilation, sometimes a desirable thing for anoxic persons, involves slightly different mechanisms according to the presence or absence of nitrogen in the inspired gas. When pure oxygen is being breathed, the effect of hyperventilation is solely that of increasing the partial pressure of oxygen at the expense of carbon dioxide. When air is being breathed, we have in addition the effect of an increased apparent respiratory quotient in causing an increase in oxygen pressure at the expense of nitrogen.

These are some of the phenomena that can only be discussed when we have an alveolar air equation or some good way of representing graphically the consequences of gas exchange in the lungs, the fundamental and inescapable basis of which is the inequality of the rates of transfer of oxygen and carbon dioxide across the alveolar membrane. Since this gas exchange is not mentioned or even implied in the definition of tracheal air, a tracheal air formulation cannot tell us anything about its consequences. On the other hand, the effects involved are usually smaller than the variation between individuals, and are for the present of scientific rather than practical interest.

Charts illustrating the composition of alveolar air at different altitudes

In chart I the partial pressures of gases are plotted together in such a manner that in every case the relationship (2) is indicated. Thus the tracheal nitrogen pressure plus 47 plus tracheal oxygen pressure add together to give an ordinate equal to the

atmospheric pressure. In the same way, the experimental averages obtained from analysis of alveolar air at the corresponding atmospheric pressures are plotted. From these curves may be seen the effect of the alveolar exchange in increasing the pressure of nitrogen in the alveolar air and decreasing the pressure of oxygen at moderate altitudes, when anoxia is not a factor. At higher altitudes a semi-steady state supervenes; the nitrogen pressure change tends first to disappear and is ultimately reversed when the stimulus of anoxia produces a sufficient increase in ventilation for carbon dioxide to be added to the alveolar air in excess of the oxygen absorbed. Charts 2 and 3 relate to the time it takes to establish a new steady state and its constancy when once established. Chart 2 provides a control, representing the behavior of the alveolar gases at an altitude - 10,000 feet - too low for the increased ventilation associated with anoxia to become important. The data given in Chart 3 were obtained for a similar group of subjects in a stay of 90 minutes at 15,000 feet. One notes the initial decrease of the nitrogen pressure to the tracheal value, a sign of increased loss of carbon dioxide, and the gradual re-establishment of a steady state resembling that found in the preliminary measurements at ground level. With increasing anoxic drive, it would require a longer time to reach a new steady state and the measurements normally made are likely to refer to a semi-steady state tending toward a final steady state which may, however, be impossible to attain and incompatible with survival. This is already the case at 15,000 feet for most of the individuals upon whom the observations averaged in Chart 1 were made, as the rising value of the alveolar respiratory quotient clearly indicates.

We may draw from the literature an extreme example of the effect described (11). The alveolar air of Douglas immediately following a period of hard work on Pike's Peak, where his alveolar oxygen in a control observation had been found to be 55 mm., had a partial pressure of oxygen of 67 mm. (see Table 1), returning in 27 minutes to 56 mm. According to Chart 1, with an atmospheric pressure of 460 mm., this must have involved an alveolar nitrogen change from the control value, 377 mm., to 368 mm. The apparent respiratory quotient at this time had become 1.35 compared to a control value of 0.86. This illustrates how the nitrogen effect predicted by the alveolar air equation contributed to the high alveolar partial pressure of oxygen observed at the moment of greatest respiratory stress.

In Chart 4 the results of alveolar air studies made on subjects breathing essentially pure oxygen at pressures equivalent to altitudes up to 42,000 feet are recorded in addition to those on Chart 1. As we mentioned above, the only effect of increased ventilation is a fall in the partial pressure of carbon dioxide which is directly reflected in an increase in the partial pressure of oxygen. A further use for this chart is in showing graphically the effect these changes in oxygen pressure during alveolar exchange have upon the idea of the equivalence of certain pairs of altitudes when the atmosphere consists of air or of pure oxygen. To begin with, let us see how the tracheal reference point can be used by inspection of this chart. Any point on the one tracheal oxygen curve can of course be compared with the corresponding point on the other, and perpendiculars from these points will give equivalent altitudes. For example, points A3, B3, or C3 may be compared with points A2, B2, or C2 respectively. It can be seen, however, by inspecting the points on the alveolar oxygen curves, that somewhat different pairs of equivalents can be obtained on the basis of equality of alveolar oxygen pressure. Points A4, B4, and C4 do indeed represent the altitudes equivalent to A1, B1, and C1 if the respiratory quotient is unity, which it might very well be if the subject had been eating candy or a meal rich in carbohydrate; but if it is much less than this, the equivalent altitudes will

be represented by points A5, B5 and C5. Considering now the A points alone, the curves indicate that there may be a difference of 1,100 feet between the results obtained by use of the two reference points. The point A6 indicates the alveolar oxygen pressure to be expected if the tracheal air is used as a reference point. We may now reverse the procedure just described in order to illustrate how those considerations may be used in determining the altitude at which a nitrogen-oxygen mixture of given composition will keep a flyer in a physiological state equivalent to that which would be expected if he were breathing air at a specified lower altitude. Let us choose 4,300 feet as our standard altitude, at which the alveolar oxygen will be given by point A6 if the R.Q. is less than 1, and the tracheal oxygen by point A3. Further let us suppose, for the sake of argument, that the curves on the right refer not to pure oxygen but to a particular mixture very rich in oxygen, and that we wish to determine how high an aviator can fly on this mixture in order to remain "physiologically" at 4,300 feet. The "tracheal" oxygen criterion gives us 35,700 feet as our desired equivalent; the alveolar criterion gives about 36,800 feet, Thus the use of the latter tends to cut the oxygen supply recommended for fulfilling a particular requirement in high altitude flying; the tracheal oxygen criterion "plays safe." But as we have already remarked, variation in individual requirements is really of greater importance than such relatively small theoretical differences as those considered here.

In concluding this section let us express our awareness that no known standard can give us tables of equivalent altitudes that are strictly valid from a physiological point of view. In the graphic construction just outlined, we define equivalence on the basis of equal alveolar partial pressures of oxygen; but clearly we ought also to include the carbon dioxide, the blood flow, and probably innumerable other factors. The calculations given by Brink and others do define equivalent altitudes as those at which both oxygen and carbon dioxide partial pressures are equal; and this does indeed provide us with calculated tables of equivalents that satisfy the theoretical conditions imposed. Examination of experimental data shows clearly, however, that at those supposedly equivalent altitudes the alveolar carbon dioxide pressures rarely are in fact equal, so that our theoretical tables confront us with a physically possible situation which does not however appear to correspond to any actual physiological one. The reason for this is not easy to find, but further research will perhaps give us the explanation. In any event, we are inclined to believe that application of the idea of equivalent altitudes should be limited to the attempt to give an aviator expecting to fly at very high altitudes some idea of the conditions he will encounter in terms of conditions already familiar to him. Attempts to refine, beyond this point, an essentially obscure idea seem hardly worth while.

Anoxia and cardiac output. From the results of alveolar gas analysis, applying the premiss (already discussed in relation to experimental evidence on page 1) that the partial pressures are reflected nearly identically in the blood passing through the lungs, we may draw certain conclusions concerning the venous oxygen pressures that are to be expected for various degrees of anoxia and various types of circulatory adjustment. For the purposes of calculation we need to take into account the following factors, and have done so in the manner indicated in each case:

(1) The normal oxygen dissociation curve of human blood and its variation with carbon dioxide pressure. This has been done by assuming an oxygen capacity of 20 volumes per cent and the dissociation curve given in L.J. Henderson's nomogram for the blood of A.V.B. (Fig. 157, ref. 14)

(2) A normal oxygen consumption, which must be maintained under all circumstances. This has been assumed equivalent to the loss of 6 volumes per cent oxygen, or 30 percentage points oxygen saturation, by blood circulating at a normal rate.

(3) A relationship between arterial and venous oxygen pressures implied by

(a) loss of 6 volumes per cent oxygen for normal blood flow or 6/N volumes per cent when the blood flow is N times normal.
(b) uptake by the circulating blood of Q times as much carbon dioxide as the oxygen lost, where Q is the alveolar respiratory quotient.

This has been done by introducing into Henderson's nomogram respiratory quotient lines in such a manner that a straight edge pivoted about a given point on one such line traverses the "total CO_2" scale and the "HbO_2" scale at rates whose ratio is Q. These lines are somewhat similar to the respiratory quotient lines in Henderson's Fig. 41.

Using these assumptions we have made calculations applicable to two extreme hypothetical conditions. First we have supposed the cardiac output to remain unchanged under conditions of anoxia. In this case, the venous oxygen pressure would have to follow approximately the course indicated by the solid line in Chart 5. We note that at about 22,000 feet it falls as low as 20 mm. Hg, a value that we are inclined to consider rather improbable and highly damaging. It is true that oxygen tensions as low as 12 mm. have been recorded in venous blood during heavy work (19) but Bainbridge (1) sets the lowest value at 20 mm. Since we are here dealing with an average that must apply to the blood supply of the nervous system, which will probably not tolerate as great a fall of venous oxygen pressure as other tissues, it is fairly safe to assume that at some point during the progressive removal of oxygen from the inspired air circulatory compensation occurs. For purposes of calculation we have assumed this to take place whenever the venous oxygen pressure falls below a certain critical value. If the critical level is set more or less arbitrarily at 28 mm. we obtain the upper relative cardiac output curve shown in Chart 5, while the lower curve applies to a critical level of 26 mm. Such estimates are necessarily subject to considerable error, but it is of interest that the scanty existing measurements of cardiac output at simulated altitudes (21), (20) fall within the range covered by these two estimates. The general but very rough plausibility of the picture may serve to indicate the need for well organized experiments which will clarify the whole situation and obviate the use of such devices as Henderson's nomogram under somewhat extreme conditions to which they do not apply with any particular accuracy. The time has come when the most urgent need is the more extended study of the character of physiological adaptation to anoxia, an end result of which is so clearly indicated by changes in the composition of alveolar air.

TABLE 1

Changes in composition of alveolar air following muscular work at high altitude (from Douglas, Haldane, Henderson and Schneider, Phil. Trans. of Royal Society of London, Series B, Vol. 203, pp. 185-318, Table VII, p. 222, 1913).

Measurements on Douglas on top of Pike's Peak, Colorado. Work consisted of maximal exertion for 45 seconds on 25% grade. Barometric pressure 460 mm.

		CO_2 (mm. Hg)	O_2 (mm. Hg)	Alveolar R.Q.
1.	Normal mean inspiration and expiration	28	55	0.86
2.	Immediately after stopping exercise	25	67	1.35
3.	10 minutes after stopping	24	59	0.82
4.	19 minutes after stopping	26	58	0.89
5.	27 minutes after stopping	25	56	0.78
6.	38 minutes after stopping	28	53	0.77
7.	50 minutes after stopping	26	53	0.79

REFERENCES

(1) Bainbridge, F.A., Book, A.V. and Dill, D.B. The physiology of muscular exercise, New York, 1931, page 141.

(2) Bateman, J.B. O.S.R.D. Committee on Aviation Medicine, Report No. 224, Dec. 1943.

(3) Bateman, J.B. and Boothby, W.M. O.S.R.D. Committee on Aviation Medicine, Report forthcoming, 1944.

(4) Henzinger, T. Ergebn. Physiol. 40, 1 (1938).

(5) Book, A.V. and Field, H. J. Biol. Chem., 62, 269, (1924).

(6) Boothby, W.M. and Robinson, F.J. O.S.R.D. Committee on Aviation Medicine, Report No. 163, June 1943.

(7) Brink, F. Essay A. in ref. (22), (1944).

(8) Campbell, J.M.H. and Poulton, E.P. J. Physiol., 54, Proc. xlix, (1920).

(9) Dill, D.B., Hurxthal, L.M. Van Caulaert, C., Poelling, A. and Book, A.V. J. Biol. Chem., 74, 303 (1927).

(10) Dill, D.B., Lawrence, J.S., Hurxthal, L.M. and Book, A.V. J. Biol. Chem., 74, 313 (1927).

(10a) Dill, D.B. War Department Report No. Exp. M 653-1034.

(11) Douglas, C.G., Haldane, J.S., Henderson, Y. and Schneider, E.C. Phil. Trans. Roy. Soc. London, 185, 2038 (1913).

(12) Gray, J.S. School of Aviation Medicine, Randolph Field, Texas: Research Report No. 1, April 12, 1944.

(13) Haldane, J.S. and Priestley, J.G. Respiration, New Haven, 1935.

(14) Henderson, L.J. Blood. A study in general physiology. New Haven, 1928.

(15) Henderson, L.J., Book, A.V., Field, H. and Stoddard, J.L. J. Biol. Chem., 59, 379 (1924).

(16) Krogh, A. and Krogh, M. Skand. Arch., 23, 179 (1910).

(17) Meakins, J.C., Dautrebande, L. and Potter, W.J. Heart, 10, 153 (1923).

(18) Peters, J.P., Barr, D.P. and Rule, F.D. J. Biol. Chem., 45, 489 (1921).

(19) Schneider, E.C. Physiology of muscular activity. Philadelphia, 1941, page 156.

(20) Starr, I. and McMichael, M. O.S.R.D. Committee on Aviation Medicine, Report No. 165, August 1, 1943.

(21) Steele, J.M. O.S.R.D. Committee on Aviation Medicine, Monthly Progress Report No. 5 on Contract No. OEMcmr-120, September 8, 1942.

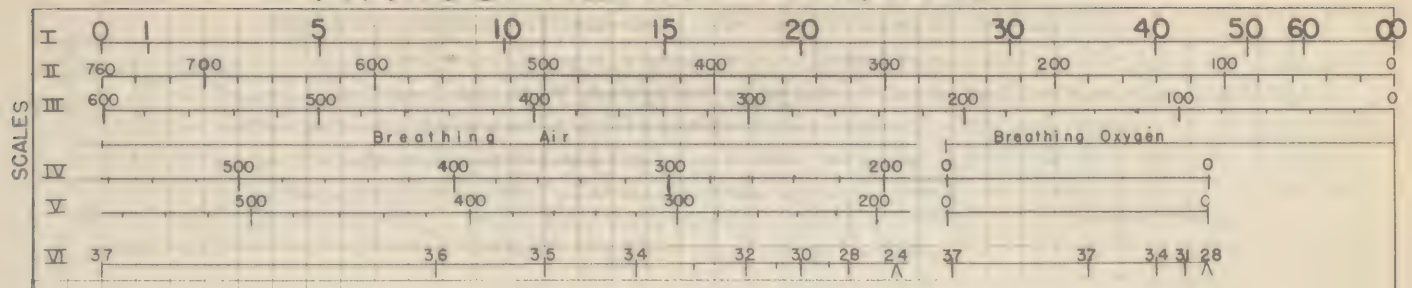
(22) Subcommittee on Oxygen and Anoxia: Handbook of respiratory data in aviation. Washington, D.C., 1944.

(23) Wildhack, W.A. J. Aeronautical Sci., 9, 543 (1942).

Fig 1

MAYO AERO MEDICAL UNIT

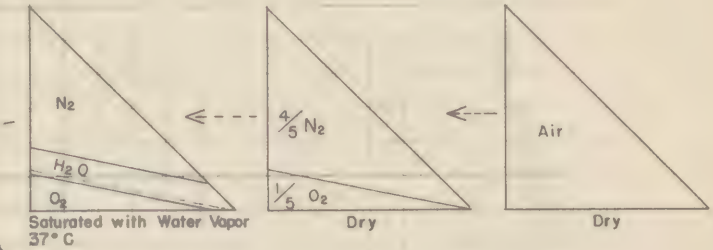
ATMOSPHERIC TRIANGLE



EXPLANATION OF UPPER SERIES OF SCALES

I Altitude 1,000 feet
II Barometric Pressure
III Partial Pressure of Nitrogen in Dry Air: (B x 0.7903)
IV Partial Pressure of Nitrogen in "Tracheal" Air after Saturation with 47 mm. Water Vapor, Body Temperature 37°C (B.T.P.S); (B − 47) 0.7903
V Partial Pressure of Nitrogen in Alveolar Air: (B − 47) Af N_2
VI Partial Pressure of Carbon Dioxide in Alveolar Air: (B − 47) Af CO_2

All Pressures in mm. Hg.



BAROMETRIC PRESSURE

The Partial Pressure of Alveolar Gases must equal Barometric Pressure

Unless A.R.Q. is Unity there is a change in the Lung of the Volume of the Respiratory Gases

As many Molecules Nitrogen are exhaled as are inhaled

Therefore a change in Nitrogen Pressure can be used to calculate the change in Volume and to obtain the A.R.Q

p = partial pressure of gas
Af. = "Atmospheric" air dry
T = "Tracheal" air (BTPS)
A = Alveolar air (BTPS)

PARTIAL PRESSURE OF GASES

760 700 650 600 550 500 450 400 350 300 250 200 150 100 50 0

NITROGEN

At. pN_2
TpN_2
ApN_2
Change in $pN_2 = ApN_2 - TpN_2$
WATER VAPOR
ALVEOLAR CARBON DIOXIDE
OXYGEN
At pO_2
ApO_2 ARQ = 1.0
ApO_2 ARQ ≠ 1.0
OXYGEN
TpO_2
Available Oxygen
BREATHING AIR

TpO_2
ApO_2
WATER VAPOR
CARBON DIOXIDE
OXYGEN
BREATHING OXYGEN

ALVEOLAR RESPIRATORY QUOTIENT

1.1 1.0 0.9 0.8

No Nitrogen available so A.R.Q. cannot be calculated

Bar. Press. 760 700 600 500 400 300 200 100 0

Alt. 1,000 Ft. 0 1 5 10 15 20 30 40 50 60 00

Chart I-6d-e

J.B. Bateman and W.M. Boothby Aug. 1944

Fig. 1 a.

Mayo Aero Medical Unit

EFFECT OF ANOXIA ON ALVEOLAR AIR PRESSURES

AVIATOR BREATHING AIR AT VARIOUS ALTITUDES

The pressures of O_2, CO_2 and N_2 in the inspired tracheal air are characteristically altered during the respiratory cycle. In the "Steady State" these respiratory changes are based upon the character of food eaten which alters not only the partial pressures but also the total volume of the alveolar air from the inspired air. Altitude anoxia, dependent upon its intensity and duration, superimposes in the "Semi - Steady State" definite additional changes in the alveolar nitrogen, oxygen and carbon dioxide pressures and consequently upon the various ratios or quotients that can be calculated therefrom. The alveolar oxygen pressure can be calculated by the following formula:

$$pO'' = pO' - \left[pC'' + (pN'' - pN')\right]$$

One prime' = Tracheal air: Two primes" = Alveolar air

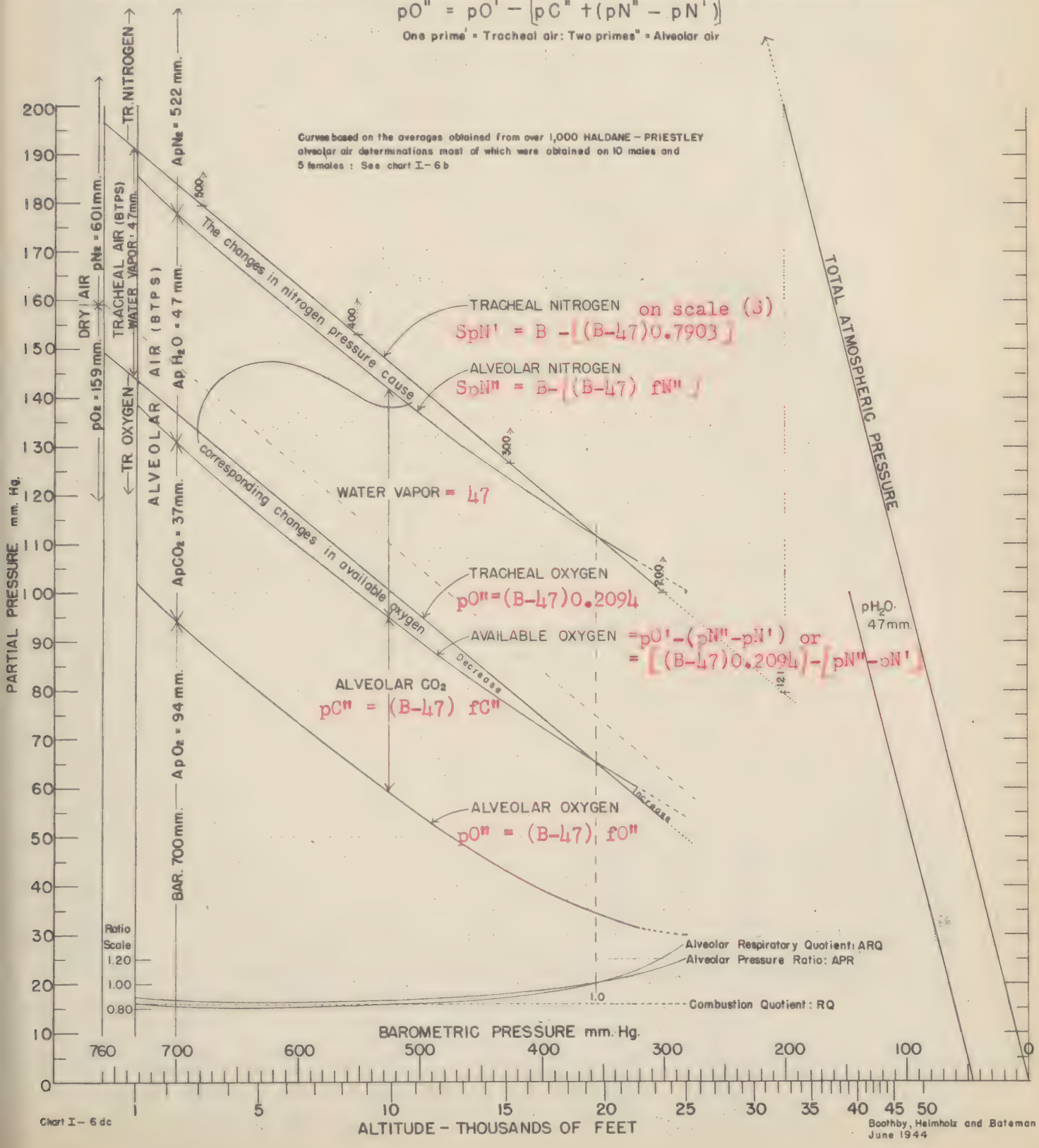


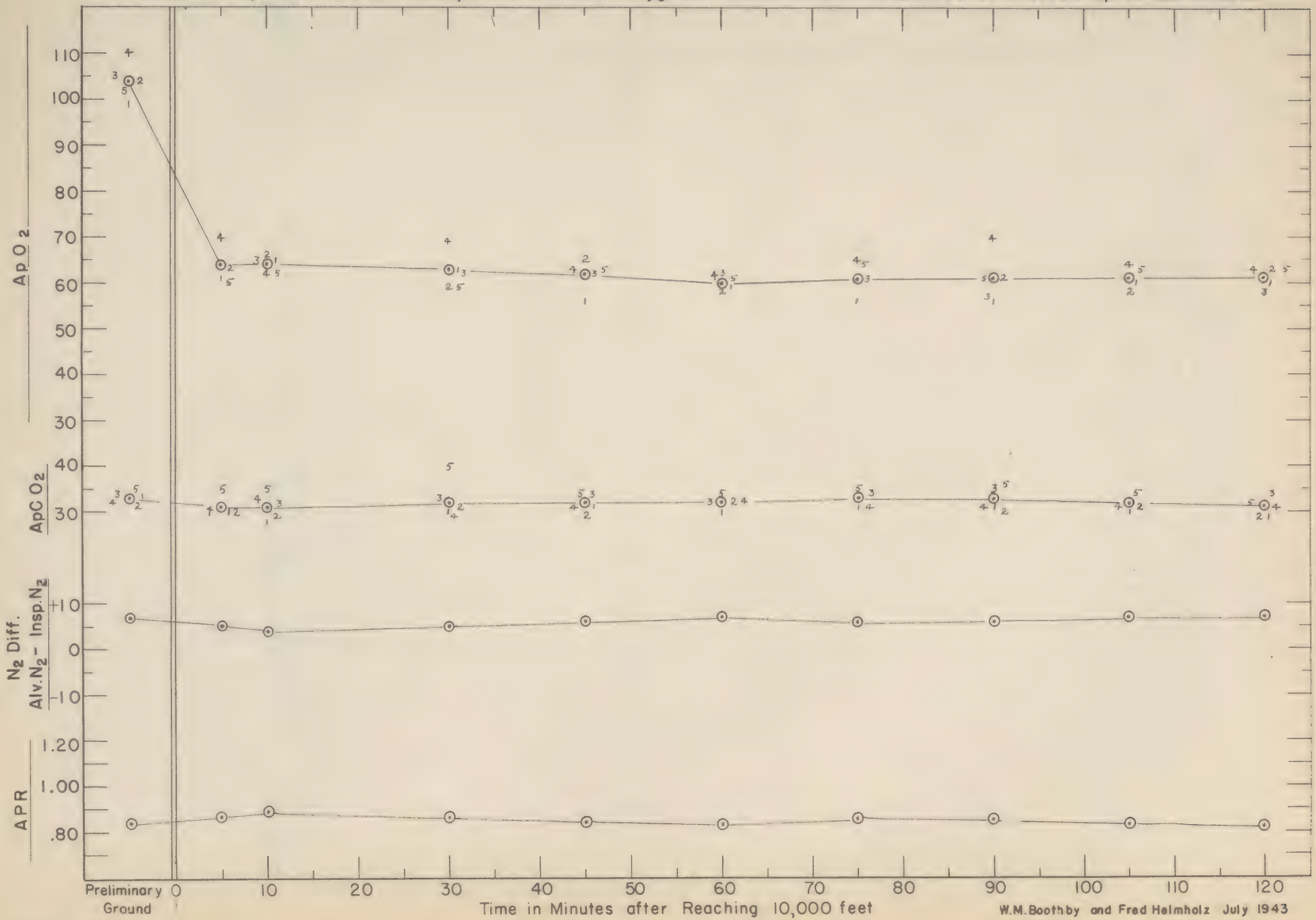
Chart I-6dc

Boothby, Helmholz and Bateman
June 1944

.Mayo Aero Medical Unit

Alveolar O_2 and CO_2 Pressures and Alveolar Pressure Ratios as affected by Duration of Stay at 10,000 feet

Five subjects were taken to 10,000 feet without oxygen. Alveolar airs were obtained at intervals up to 120 minutes



W.M. Boothby and Fred Helmholz July 1943

Chart I — 10 b

Fig 3

Mayo Aero Medical Unit

Alveolar O_2 and CO_2 Pressures and Alveolar Pressure Ratios
as affected by Duration of Stay at 15,000 feet

Six subjects went to 15,000 feet without Oxygen. Alveolar airs were obtained at intervals up to 90 minutes

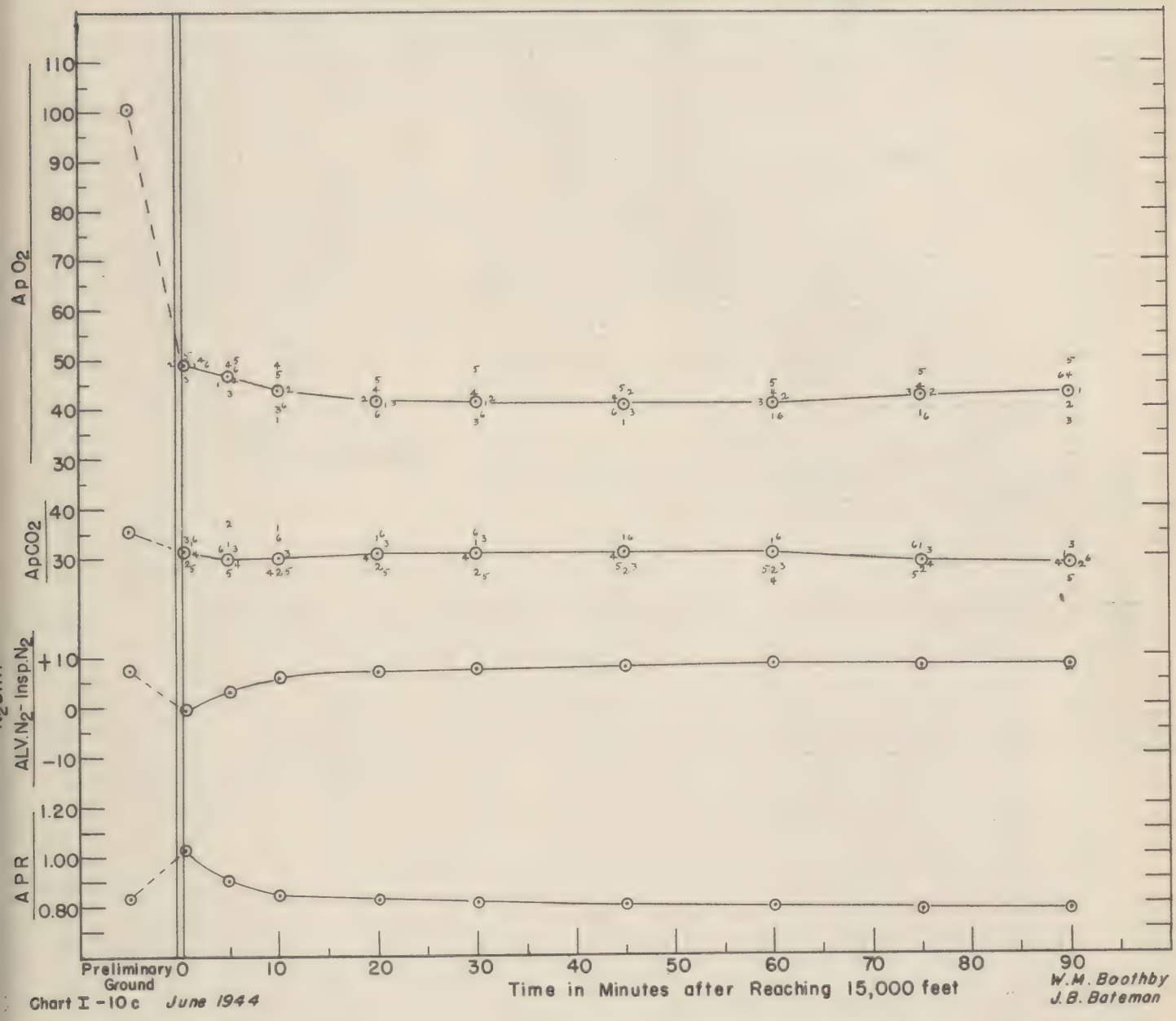


Chart I - 10 c *June 1944*

W. M. Boothby
J. B. Bateman

Fig 3a

MAYO AERO MEDICAL UNIT

Alveolar O_2 and CO_2 Pressures and Alveolar Pressure Ratios as affected by Duration of Stay at 15,000 feet

Five subject were taken to 15,000 feet on "normal" oxygen, about 10 minutes at altitude mask was removed and alveolar airs obtained at intervals up to 90 minutes

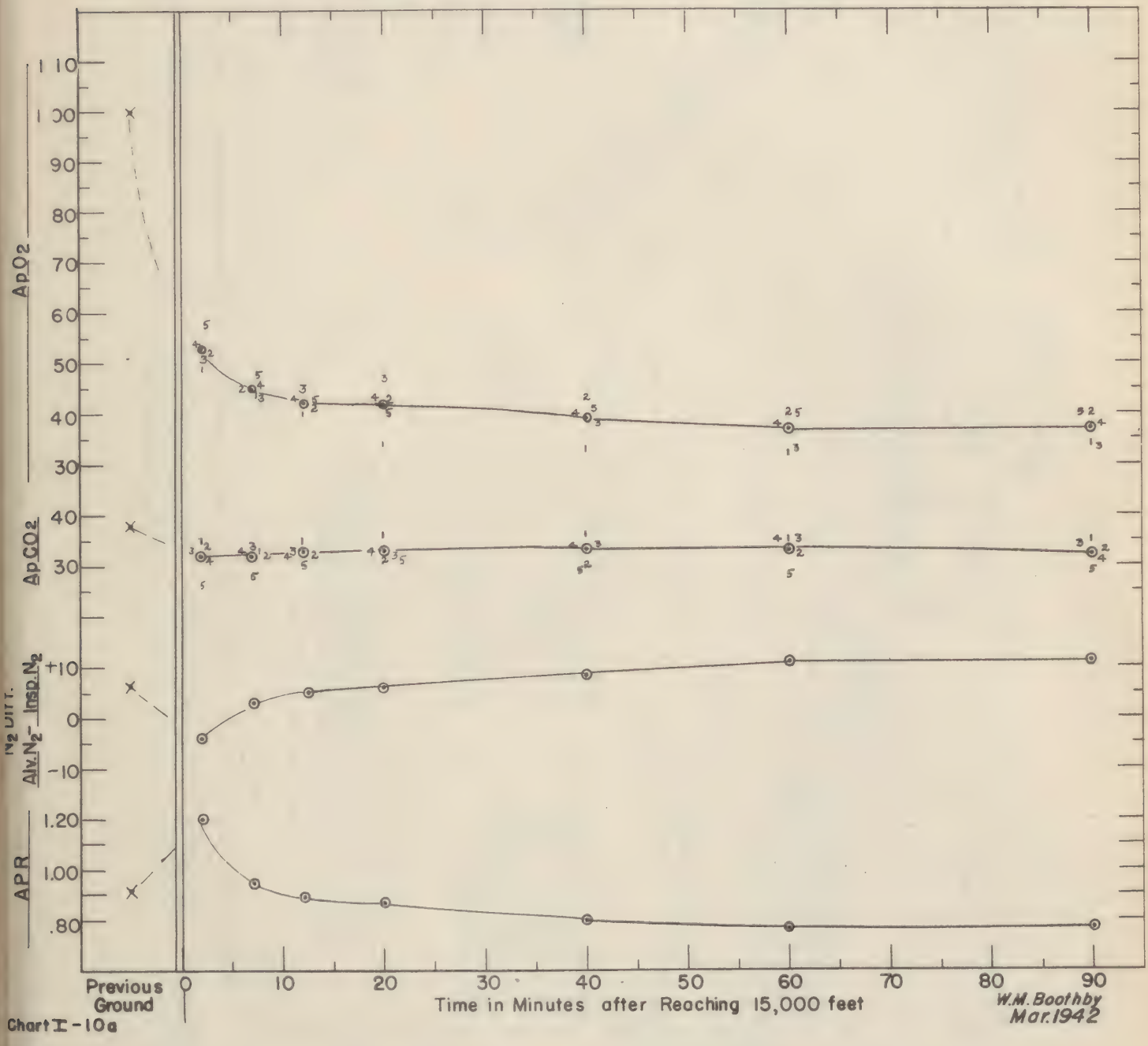


Chart I-10a

MAYO AERO MEDICAL UNIT

COMPARISON BETWEEN LOW ALTITUDES BREATHING AIR AND HIGH ALTITUDES BREATHING OXYGEN

based on over 1400 determinations of the alveolar air by the Haldane – Priestley method on subjects acclimatized to ground level of 1000 feet

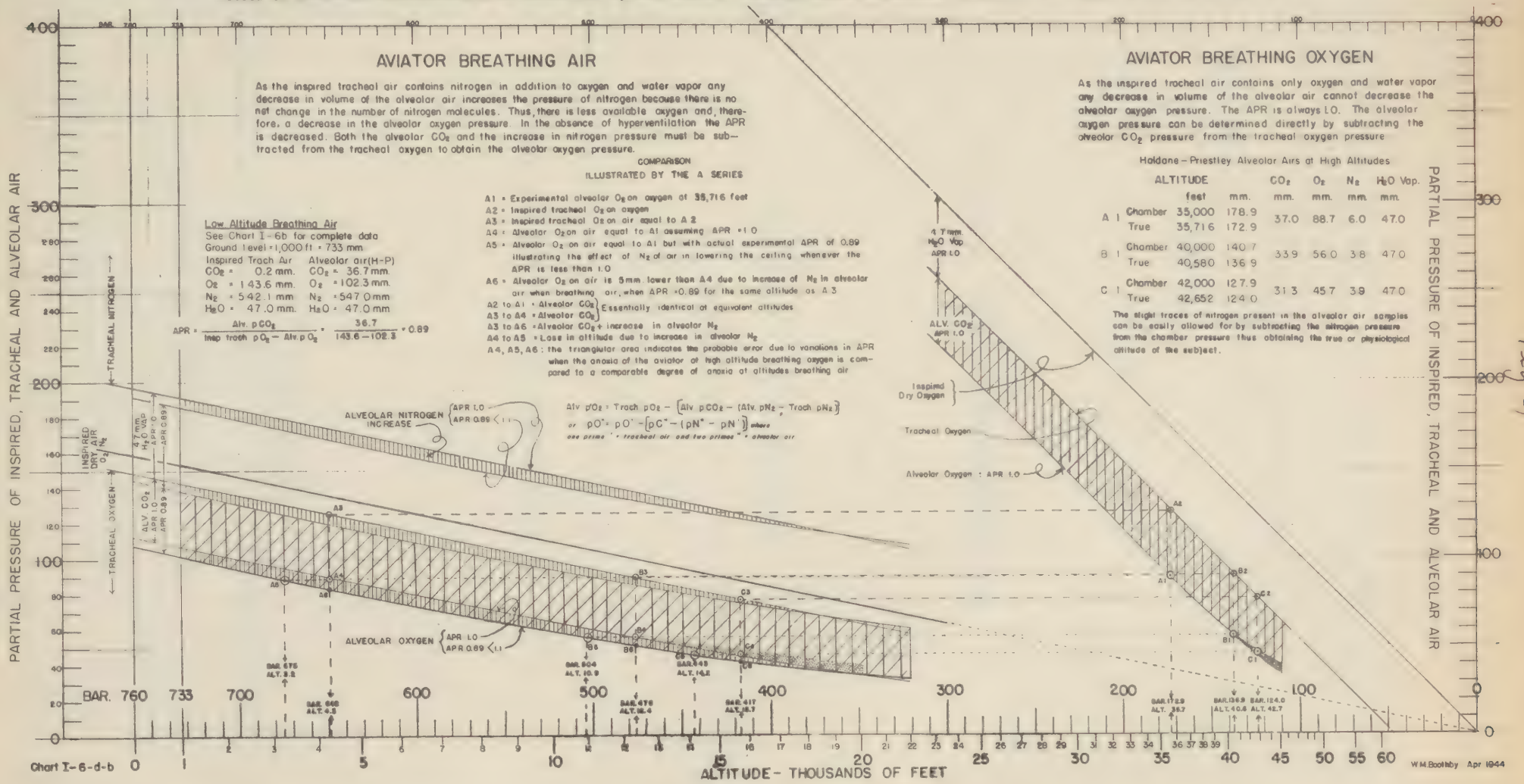


Fig 4

Fig 5

MAYO AERO MEDICAL UNIT

INCREASED CIRCULATION RATE WITH ANOXIA

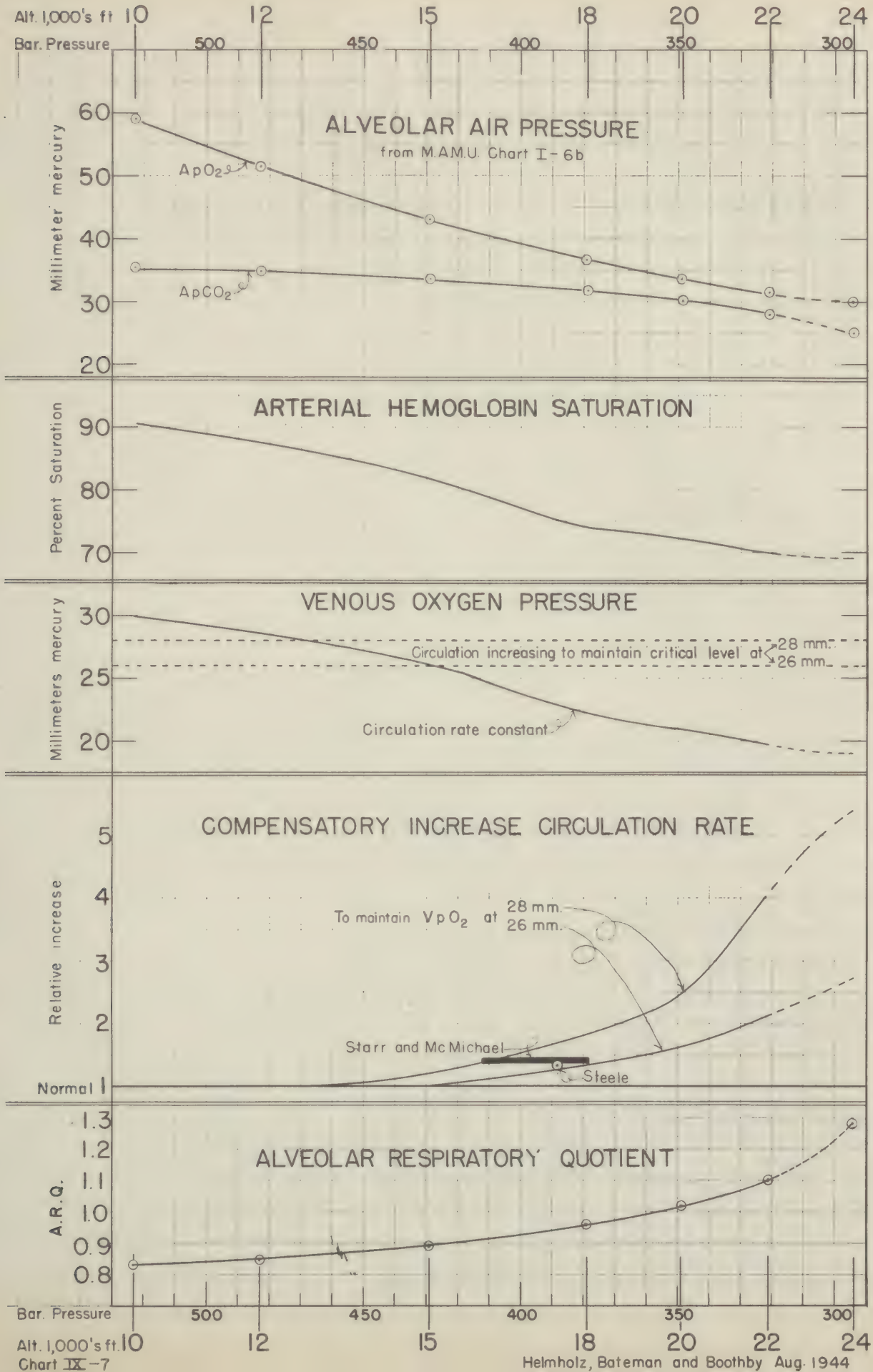


Chart IX-7

Helmholz, Bateman and Boothby Aug. 1944

NATIONAL RESEARCH COUNCIL, DIVISION OF MEDICAL SCIENCES

acting for the

COMMITTEE ON MEDICAL RESEARCH
of the
Office of Scientific Research and Development

COMMITTEE ON AVIATION MEDICINE

Report No. 364
September 1944

SUSCEPTIBILITY TO DECOMPRESSION SICKNESS: THE EFFECTS OF PROLONGED INHALATION OF CERTAIN NITROGEN-OXYGEN MIXTURES COMPARED WITH THOSE OF EXPOSURE TO PURE OXYGEN.
From the Mayo Aero Medical Unit, Rochester, Minnesota, by J.B.Bateman.
Responsible Investigator: Walter M. Boothby.

SUMMARY

The responses of four experimental subjects to partial nitrogen elimination produced by prolonged inhalation of certain nitrogen-oxygen mixtures have been compared with the effects of brief exposures to pure oxygen. The responses were measured by estimating the susceptibilities of the subjects to decompression sickness during a 40 minute flight, with physical exercise, at 35,000 feet. The experiments had a practical and a more academic aspect:

Problem (i): A person flies at 15,000 feet for about six hours, breathing air sufficiently enriched with oxygen to make his alveolar oxygen pressure about equal to its usual value (a) at sea level and (b) at 5,000 feet. How much protection from "bends" will these procedures afford if the subject then ascends to 35,000 feet?

Results: Inhalation of 40 per cent oxygen for six hours at 15,000 feet (sea level standard) protected three of the four subjects almost completely; in the most susceptible subject the amount of protection was hardly significant. In all cases the amount of protection was about the same as that afforded by pre-oxygenation at ground for 100 minutes. Thirty per cent oxygen (5,000 feet standard) was somewhat less effective. Thus individual differences are still apparent after six hours desaturation, so that the selection of personnel for missions of the type simulated in these experiments should include measurement of the response to pre-oxygenation. It is also recommended that oxygen regulators be set at a sea level rather than a 5,000 foot standard.

Problem (ii): Are individual differences in response to pre-oxygenation due primarily to differences in the rate of elimination of an "effective" or symptom-producing nitrogen fraction, or are they due to the operation of other factors which facilitate the production of symptoms in some individuals at lower nitrogen levels than in others?

Results: (i) "Calibration" by inhaling pure oxygen: the well-known effects were shown. Three subjects were completely protected after inhaling oxygen for 110 minutes; the fourth required more than six hours.

(ii) "Equilibration" with a given partial pressure of nitrogen required at least six hours for three subjects and at least twelve hours for the fourth.

(iii) The slow removal of a given fraction of the total dissolved nitrogen probably confers equal protection upon all subjects, regardless of differences in their response to pure oxygen. Thus removal by true equilibration of about 70 per cent provides nearly complete immunity; removal of 50 per cent gives considerable protection; removal of only 30 per cent gives slight but measurable protection.

(iv) The threshold for production of symptoms at 35,000 feet appears to be about 230 mm. Hg for dissolved nitrogen. The theoretical threshold for growth of a bubble at this altitude is about 60 mm.

(v) By comparing the "equilibration" data with the curves for protection by brief exposure to pure oxygen, it is possible to construct elimination curves for the symptom-producing nitrogen without having recourse to conventional nitrogen elimination measurements. The half-desaturation times obtained in this manner were about 100 minutes, or more, for three subjects, and 260 minutes, or more, for the fourth. The former value is not greatly different from the accepted overall values for nitrogen elimination; the latter is much greater.

(vi) The data, although extremely limited, thus appear to vindicate the hypothesis of a slowly eliminated nitrogen fraction as the cause of symptoms of decompression sickness.

NATIONAL RESEARCH COUNCIL, DIVISION OF MEDICAL SCIENCES

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By J. B. Bateman from the Mayo Aero Medical Unit, Rochester, Minnesota.
Responsible Investigator: Walter M. Boothby.

1. INTRODUCTION.

The well-established effect of oxygen in reducing or even abolishing the hazard of decompression sickness upon subsequent decompression provides the strongest available evidence for the supposition that the symptoms of this condition are closely correlated with the presence in the body of gas bubbles which owe their ability to increase in size, if not their actual existence, to the establishment of a physically definable relationship between the concentration of dissolved nitrogen in the body and the prevailing barometric pressure. The detailed picture is however far more obscure than this simple view would imply, and one of the sources of difficulty lies in the existence of individual differences in the degree of immunity developed by brief exposure to oxygen - differences far greater than might be expected from the rather scanty available records of the rates at which dissolved nitrogen is eliminated during the breathing of oxygen. For this and other reasons it has been suggested that although the overall rates of nitrogen elimination do not exhibit the required range of values, there may exist in the body slowly desaturating localities for which time constants are not open to estimation by any existing direct method. However, our knowledge of the factors which influence the production and growth of bubbles, both in vitro and in the animal body, is sufficiently advanced to suggest that the hypothesis of slowly desaturating regions may be superfluous. This possibility is amenable to direct experimental test, for if there are slowly desaturating regions, the response to elimination of a given fraction of the total body nitrogen should depend upon the time in which this is accomplished, the distribution of the remaining nitrogen tending to become more uniform in course of time. It would follow that elimination of a given fraction of body nitrogen by brief exposure to pure oxygen should be less effective in preventing the symptoms of decompression sickness than elimination of the same amount of nitrogen by prolonged inhalation of a suitable nitrogen-oxygen mixture. It would further be expected that the latter procedure would tend to obliterate or diminish the individual differences that have been so strikingly demonstrated by the usual procedure of pre-oxygenation. If, on the other hand, the slowly eliminated nitrogen fraction is not of prime significance, one would expect the same response to elimination of a certain proportion of nitrogen whatever time course is followed, and consequently the same individual differences.

In the present experiments we endeavoured to find a preliminary answer to the problem posed in the above terms. The first impetus to the project was provided by a practical question drawn to our attention by Dr. Code upon his return from a meeting of the Committee on Decompression Sickness. A person flies at 15,000 feet for about six hours, breathing air sufficiently enriched with oxygen to make his alveolar oxygen pressure about equal to its usual value at sea level. How much protection from "bends" will this procedure afford if the aviator then ascends to 35,000 feet? A very good guess can be made, and was in fact made by Code and Robinson (1944); it could be confidently predicted that the preliminary flight at 15,000 feet would protect the fliers to a significant extent, but the amount of protection could not be expressed in terms of the equivalent period of breathing pure oxygen, nor could it be stated to what extent individual differences in behavior would be encountered. Thus solution of the operational problem would be a step toward clarification of the questions of mechanism just adumbrated, and it seemed opportune to extend the experiments somewhat beyond the stage demanded by practical considerations.

We believe that the results presented below justify a fairly definite statement concerning the protective effect of long exposure to various gas mixtures prior to high altitude flight, and that the implications of the results in terms of the relative importance of "slow" nitrogen and other, undefined, factors are suggestive enough to warrant further work along the same lines. We have been hampered by our very limited access to experimental subjects; a limitation that is, however, significantly offset by the increased reproducibility of decompression sickness data that results from the use of a standardized exercise for accelerating the production of symptoms. On the other hand, it must be remembered that an essentially different analysis might be necessary for the interpretation of data obtained without this facilitating influence.

2. METHODS.

Most of the experiments were carried out with four subjects, whose pertinent physical characteristics are given in Table 1. The general procedure prior to the actual susceptibility test was always the same apart from differences in time, altitude, and composition of inhaled gas. The subjects breathed the appropriate gas mixture through a constant flow apparatus and ASB mask in which the usual sponge rubber discs were usually replaced by expiratory valves, the flow being adjusted to a somewhat excessive value in order to avoid the possibility of inward leakage of air. During six-hour periods of breathing under these conditions intervals were usually taken at the end of two and four hours, and at these times it was considered justifiable to allow the subjects to breathe air for 10 or 15 minutes. At the end of this preliminary period the subjects were taken rapidly (5,000 feet per minute) to a simulated altitude of 35,000 feet. The standard exercise which was used during these high altitude flights was commenced at 20,000 feet during ascent; it consisted of five deep knee bends and five arm bends (with subject holding 3 lb. weights) every three minutes. The entire record of each experiment was kept on a series of standardized sheets consisting of (1) a questionnaire which was addressed to the subject by the outside observer immediately before ascent to 35,000 feet, (2) a record of symptoms, resembling in many ways that used by the Yale Aero Medical Unit (1944), which was filled in during the run by the subject, (3) a record kept by the outside observer during the run, and (4) a questionnaire which was addressed to the subject upon descent to ground. The estimate of susceptibility used in the final analysis of the data was based almost entirely upon the subjective record, the records kept by the observer being used mainly as

a precautionary measure in following the course of objective manifestations. The subjects were instructed to locate their symptoms on a drawing of the body and to grade them according to severity, time of onset, and duration. They were aware that the object of the experiments was to determine their susceptibility to decompression sickness rather than to test their powers of endurance, and that they were therefore expected to descend to ground in the look as soon as their symptoms approached the stage at which assistance from their fellows might become necessary. For those subjects who were either without symptoms or who were able to stay at altitude for 90 minutes, the flight was terminated at this time. All subjects were questioned at the end of the run in order to determine whether or not after-effects were present or were to be anticipated; the questions related to the possible presence of disturbance of vision, headache, respiratory difficulty, nausea, skin reactions, and persistent pain. The pulse was counted.

Concerning the subjective statement of severity of symptoms, we found that it was not possible to distinguish reliably between more than four grades. These were described as follows:

Grade 1: mild, definite.
2: moderate, and somewhat distracting with exercise.
3: moderate, preventing exercise.
4: incapacitating, necessitating descent.

These records were used in the following way in obtaining a numerical value related to the degree of the subject's immunity to symptoms. Four points were allotted for every minute during which the subject was free from symptoms at 35,000 feet. Grade 1 pains were given 3 points per minute, grade 2 pains 2 points, grade 3 pains 1 point. Thus the sum of the points allotted, which we call the "recorded score" or "degree of immunity," is a function of the time of onset of symptoms, their severity and their duration. Whenever a subject was forced to descend before the end of the 90 minute experimental period, the recorded score may be considered a valid measure of immunity. In all instances in which the subject remained at 35,000 feet for the full 90 minutes, whether with or without symptoms, the recorded score is smaller than the correct score, because the subject could have continued to gain points by remaining at altitude for more than 90 minutes if the experiment had not been arbitrarily terminated. The highest possible recorded score is 360, for a 90 minute run in which the subject remains free from symptoms.

3. GENERAL COMMENTS.

(a) The standard exercise used in these experiments was somewhat too severe. During the longer flights at 35,000 feet there was considerable fatigue and joint pain which could be confused with the "bends." Occasionally it was necessary to attempt to distinguish between these possible sources of pain by ascending to 40,000 feet at the end of the run.

(b) Nature and disposition of symptoms: By far the most usual symptom was real or referred joint pain in the knees. Of a total of 90 recorded symptoms 28 were in the right knee, 29 in the left knee, 3 in the right elbow and 1 in the left elbow. On the other hand, it may be mentioned that the subject, L.C., who in these experiments was entirely free from joint pain in the arms, has suffered from severe pain in the left elbow when lifting heavy sampling sets in other experiments at 35,000 feet. Ferris, Webb, Ryder, Engel, Romano and Blankenhorn (1943) have

already drawn attention to the importance of muscular activity in electing the site of bends. The only other important and common symptom encountered was substernal discomfort, which occurred in varying degrees in three out of the four subjects. It was regarded by them as a warning of the rapid onset of chokes (compare Behnke, Welham and Yarbrough, 1942), and was accordingly considered sufficient reason for immediate descent. On account of this attitude, which was encouraged (perhaps unwisely), there were only three cases of severe chokes and eleven in which incipient chokes was given as the reason for descent. Of the remaining 21 symptoms, 7 were skin reactions (itching, erythema), occurring in several instances on the shoulders and usually appearing when substernal discomfort was also reported. The other 14 symptoms occurred mostly in one subject, R.S., who complained of nausea and of sore or tender spots on thigh and knee. One subject usually experienced tingling or pricking sensations in the arms, legs and shoulders during exercise some time before the onset of pain.

(c) After-effects: Joint pain rarely survived recompression; it usually disappeared at about 20,000 feet. It was sometimes succeeded by a feeling of weakness in the legs. The symptoms we have described as that of incipient chokes was almost invariably protracted and for an hour or two after descent the subject would complain that deep inspiration was accompanied by pain and a desire to cough. The post-flight reactions were more severe in cases of incapacitating chokes. In addition to the substernal discomfort and feeling of exhaustion there was headache, nausea, and diffuse erythema about the neck. On one occasion the reaction lasted several days, and on the day following the experiment was described by Dr. Code, who was kind enough to examine the subject, as a bilateral and symmetrical swelling of the deltoid muscles at the apex of the deltoid attachment. The swelling was hard and tender and apparently edematous. Such reactions have been seen in this laboratory on other occasions. Neurological mapping of the affected area in one case revealed no demonstrable relationship to nerve distribution. Vascular origins were not excluded.

4. RESULTS.

(a) The complete results are given in Table 2. It is not implied that we wish to give equal weight to the reports of all four subjects and the data derived from them. The recorded scores for two subjects, L.C. and J.B., are in general more consistent than the rest. The irregular behavior of subjects R.H. and R.S. can in part be accounted for, but no reliable corrections can be made. Subject R.H. was quite inexperienced, quite unfamiliar with the symptoms of decompression sickness, and inclined to be apprehensive in the earlier experiments. Subject R.S. was probably too much influenced by the suggestion that a run should be ended before incurring too great a risk of real disablement, with its increased hazard of serious after-reactions; her reasons for descent were often rather ill-defined and on several occasions it is fairly certain that she could have remained longer at 35,000 feet, perhaps considerably longer, without untoward effects. In the tables which follow we indicate recorded scores which are known, for incontrovertible reasons, to be lower than the "correct" scores, by the sign +, and to indicate those in which this is for good, but not wholly objective, reasons presumed to be the case, by the same sign in parentheses: (+). Similarly in the diagrams the corresponding points or levels are indicated by arrows in full and in broken lines, respectively. This procedure as a rule alleviates the unpleasant impression of great variability given by the data for R.S. and R.H., and makes it possible to give these data some consideration in conjunction with the apparently more reliable inference drawn from the reports of the other two subjects.

(b) The effects of inhaling pure oxygen are shown graphically in Fig. 1, in which the score is plotted against time of pre-oxygenation. More or less successful attempts have been made to draw smooth curves through the experimental points, the difficulty of this operation having been evaded in one case (R.H.) by drawing two curves which may represent approximately the limits of variability of the subject. These curves illustrate the well-known effect of inhaling oxygen. Attention is drawn to the fact that while there are no very great differences in the initial susceptibility of the four subjects, there are enormous differences in the ease with which they are protected by breathing oxygen. For three out of four subjects, 110 minutes oxygen was usually sufficient to provide complete protection under the conditions of these experiments, while in the fourth subject this result was only achieved after more than six hours.

(c) The effects of six hours exposure to 40 per cent and 30 per cent oxygen at 15,000 feet and to 40 per cent and 60 per cent oxygen at ground level are seen in Table 2. In three subjects the 40 per cent mixture at 15,000 feet gave complete protection in four runs out of six, and very considerable protection in the other two. In the fourth and most susceptible subject the amount of protection attained was measurable but hardly significant from a practical point of view. It is instructive to express the scores in these experiments in terms of the period for which pure oxygen would have to be inhaled in order to give the same degree of immunity. These periods can be read off both from the smooth curves of Fig. 1 and from similar curves made with a logarithmic time scale, in the manner indicated for the latter case in Fig. 2, and their mean values are given in Table 3. It seems probable that the equivalent periods are about the same for all subjects, and not greatly different from 100 minutes, although the score of 360 reached in several instances makes the upper limit of the equivalent period somewhat indefinite.

The single experiment in which two subjects breathed 30 per cent oxygen for six hours at 15,000 feet showed this mixture to be appreciably less effective for L.C. than the 40 per cent mixture; in the latter case the full score was reached in a 90 minute run, while after the 30 per cent mixture the subject, although able to stay the full 90 minutes without particular discomfort, was bothered by a skin reaction (itching, redness and slight swelling) which persisted for some hours after descent. The second subject's score for 30 per cent oxygen (106) lies within the range of values obtained in the two experiments on 40 per cent oxygen (mean 115).

Let us examine the data for inhalation of 40 per cent and 57 per cent oxygen at ground level from the same point of view. Here the full score was in no case reached. The results (Table 4) suggest that for two and perhaps three subjects, including the most susceptible one, six hours inhalation of 40 per cent oxygen at ground level is equivalent to about 50 minutes on pure oxygen. The corresponding period for 57 per cent oxygen is perhaps about 100 minutes, but the aberrant value 158 minutes for J.B. is not attributable to any known source of error apart from the flatness of the pre-oxygenation curve for this subject.

According to the Handbook of Respiratory Data in Aviation (1944) Chart A-2, an individual breathing 40 per cent oxygen at 15,000 feet is likely to have an alveolar oxygen pressure slightly higher than the normal value at sea level; such a mixture is possibly 2 per cent richer in oxygen than that supplied by a regulator adjusted to maintain a sea level standard of alveolar oxygen pressure. Concerning the probable effect of a six hour flight at 15,000 feet under such conditions upon the hazard of decompression sickness accompanying subsequent ascent to 35,000 feet, it seems

reasonable to conclude that the amount of protection will be virtually the same as that observed with 40 per cent oxygen in the present experiments at simulated altitudes. This means protection equivalent to that achieved by breathing oxygen for a little less than 100 minutes, with individual differences of the same order as those already familiar from pre-oxygenation experiments. For many, and probably the majority of flying personnel, ascent to 35,000 feet for 90 minutes will be perfectly safe; for the more susceptible individuals, it will be very hazardous. It is obvious that the latter group should not be permitted to fly on missions of this type.

The 30 per cent mixture at 15,000 feet contains possibly 2 per cent oxygen less than is needed to maintain a 5,000 foot alveolar oxygen level, the equivalent altitude breathing air being about 6,500 feet. Our test with this mixture was therefore a little too severe, but it is probable that the proportion of individuals completely protected by a 6 hour flight at 15,000 feet with oxygen applied on the 5,000 foot standard will be significantly less than if the sea level standard is maintained. Accordingly we suggest that on missions of this kind it would be advisable to arrange for the oxygen supply to conform to the sea level standard.

(d) Comparison of six hour and twelve hour experiments: If it could be assumed that in six hours equilibration between the alveolar gas and the body is virtually complete with respect to dissolved nitrogen, it would follow from the conclusions of the foregoing paragraph (c) that all four subjects have closely similar nitrogen elimination curves, and that presence of a given fraction of ground level nitrogen can be associated in different individuals with widely different susceptibilities to decompression sickness.

This point is readily put to experimental test by prolonging the period of exposure to nitrogen-oxygen mixtures. It was convenient only to perform these additional experiments on the most susceptible subject, breathing 40 per cent and 60 per cent oxygen at ground for twelve hour periods before ascent to 35,000 feet. The results in Table 2 show quite clearly that the additional six hours results in further protection. This is not quite unequivocal in the case of the 40 per cent mixture, the change being in the right direction but within the limits of experimental error, in the flat part of the curve in Fig. 1; but it is quite definite for the 60 per cent mixture, bringing the score on to the steep part of the curve, where comparatively small increments in the time of exposure to oxygen produce considerable changes in score. Thus it becomes obvious that the gross individual differences in the effectiveness of exposure to oxygen for similar periods are due largely, if not wholly, to differences in the rates of nitrogen elimination.

(e) Fraction of body nitrogen lost after equilibration with nitrogen-oxygen mixtures: For the approximate purposes of the present paper, we shall assume that for the three subjects, L.C., R.S. and R.H., six hours inhalation of any gas mixture is sufficient for equilibration between alveolar gas pressures and the potentials of dissolved gases throughout the body to be virtually complete. Since these subjects are all completely protected from "bends" by about two hours exposure to oxygen, this assumption is probably justified as a rough and ready basis for the considerations which follow. For the remaining subject, J.B., we shall assume the required period to be at least twelve hours.

The fraction of the nitrogen normally present in the body at ground level which remains after complete equilibration at a given altitude with a gas mixture other than air can readily be calculated. We have used the familiar alveolar air equation in order to find the partial pressure of nitrogen in the alveoli:

$$pO'' = pO' (1 - pC''/\bar{P}) - (1 - pO'/\bar{P}) \cdot pC''/Q$$

and $pN'' = \bar{P} - (pO'' + PC'')$

where pO' is the partial pressure of ~~nitrogen~~ oxygen in moist inspired air at 37° C.,

pO'', pC'', pN'' are alveolar partial pressures of oxygen, carbon dioxide and nitrogen; pC'' has been taken as 37 mm. Hg.

$\bar{P}$ is $(P - 47)$, P being barometric pressure,

Q is respiratory quotient, assumed equal to 0.85.

The value of pN'', thus calculated, has been assumed to be the partial pressure of dissolved nitrogen throughout the body. This has been expressed as a fraction of the value given by Boothby's analyses (1944) for subjects acclimatized to an altitude of 1,000 feet.

The scores obtained after such equilibration are given in Table 5. For three subjects, removal by true equilibration of about 60 per cent of the total dissolved nitrogen initially present in the body is sufficient to provide complete, or nearly complete, immunity to decompression sickness during a 90 minute run with exercise at 35,000 feet; removal of 50 per cent gives considerable protection to at least three subjects, including J.B., the most susceptible; removal of only 30 per cent gives slight but measurable protection. Within the limits of experimental error, it may be said that all four subjects, whether or not they happen to be easily, or only with difficulty, protected by inhalation of pure oxygen, are equally protected when they have lost an equal proportion, equally distributed throughout the body, of their total normal body nitrogen. They differ from one another only in the rate at which this nitrogen is eliminated.

(f) Nitrogen elimination curves obtained from data on decompression sickness: is the bends-producing nitrogen identical with the nitrogen collected during nitrogen elimination measurement? The data in Tables 1 and 5 and in Fig. 2 enable us to obtain points on an "apparent" nitrogen elimination curve derived solely from data on decompression sickness, without recourse to rates of nitrogen elimination obtained by direct measurement. For example: 100 minutes breathing pure oxygen is sufficient to cause a degree of immunity equal to that obtained by an "equilibration" involving retention of only 0.39 of the nitrogen originally present in every part of the body. Therefore, 100 minutes is the time required to eliminate 61 per cent of that part of the total nitrogen responsible for production of symptoms. Other points can be obtained in a similar manner for the equilibration data with 40 per cent and 50 per cent oxygen at ground level, and they can be combined on a chart which represents the rate of elimination of the "effective" nitrogen. The "effective" nitrogen may or may not be eliminated at the same rate as the total nitrogen; this can however be tested by comparing the "effective" elimination curve with the results of direct measurement. Fig. 3 contains points derived as described from our experimental data; the smooth curves have been plotted from nitrogen elimination data obtained by Behnke and Willmon (1941) and by Boothby, Lovelace and Benson (1940).

The diagram shows what has been expressed qualitatively in preceding sections: the relatively slow elimination of "effective" nitrogen in the most susceptible subject. This difference may be expressed in terms of a half-elimination time, indicated by the dotted curve, of about 260 minutes, compared with 50-100 minutes for the other three subjects. The latter range of values, moreover, is in approximate agreement with measured nitrogen elimination curves; while the former,

260 minutes, is greater than any value that has to our knowledge been recorded from direct measurements of nitrogen elimination rates. Actual measurements on this particular subject are not available, but the evidence points to the conclusion that the "effective" nitrogen and the "total" measured nitrogen are not identical in this instance.

In order to make use of the results of six hour experiments on the most susceptible subject we have argued as follows: (1) For the other three subjects, immunity to decompression sickness is attained when 60 per cent of the body nitrogen has been removed in the six-hour equilibration experiments. (2) Exposure to pure oxygen for two hours produces the same result. (3) The same result is produced in the fourth subject by breathing pure oxygen for six hours. (4) Therefore 60 per cent of this subject's "effective" nitrogen is removed in six hours. (5) Consequently in six hour experiments with nitrogen-oxygen mixtures, the fraction of original nitrogen removed is 60 per cent of that calculated as the "equilibrium" value.

The data so calculated are given in Table 6, and in Fig. 3 in the form of small half-shaded circles. They are in complete harmony with the dotted curve based upon the twelve-hour points, and thus constitute confirmatory evidence for the interpretation given above.

(g) What degree of supersaturation is necessary for the production of decompression sickness? Table 5 also gives the probable partial pressures of dissolved nitrogen in the body after equilibration under various conditions. Apparently our subjects are nearly immune to decompression sickness under the conditions of the present experiments when the potential of dissolved nitrogen in the most slowly desaturating regions of the body is equivalent to a gas pressure of about 230 mm. Hg. The barometric pressure at 35,000 feet being about 180 mm., a bubble of gas in constant equilibrium with the carbon dioxide, oxygen and water of the tissues, and sufficiently large for capillary effects to be negligible, would be able to grow by access of gaseous nitrogen if

$$\Phi N > 180 - (pC + pO + 47) + 30$$

where N, C, O refer as before to nitrogen, carbon dioxide and oxygen. ΦN is identical numerically to the pressure pN of gaseous nitrogen which would be in equilibrium with the dissolved nitrogen of the tissues. Capillary pressure is taken as 30 mm. Hg. Putting (pC + pO) equal to about 73 mm., the condition for growth becomes

$$\Phi N > 90.$$

The considerable difference between this limiting value and the experimental threshold for production of symptoms, 230 mm., shows that considerable supersaturation - roughly fourfold - can be tolerated in the body. Whether this fact arises from difficulties in the inception of bubbles, from the operation of capillary forces, or from physiological tolerance of bubbles below a certain size, it is beyond the scope of the present experiments to indicate.

5. DISCUSSION.*

The realization that many individuals are only protected against decompression sickness by rather long periods of oxygen inhalation is comparatively

* No effort has been made to refer to all the available evidence nor to give a complete bibliography.

recent. Haldane and others among the early workers on caisson sickness were aware that denitrogenation rates of various tissues would be expected to depend both on the quantity of nitrogen dissolved and on the vascularity of the tissues concerned, but they considered that adoption of a half-saturation time of 75 minutes would give generous latitude for desaturation rates below those which had at that time been detected by direct measurement. Improved measurements, notably by Behnke and his collaborators, have suggested that the greater part of the nitrogen elimination in man occurs with a half-desaturation time of 50 - 90 minutes. On the other hand, there are records of persons who required from four to six hours preoxygenation in order to acquire reasonable immunity to decompression sickness (cf. Behnke, Welham and Yarbrough, 1942; Ferris, Webb, Ryder, Engel, Romano and Blankenhorn, 1943), while for others - the majority - one to two hours is sufficient. It was natural to postulate differences in nitrogen elimination rates in order to account for this wide spread of susceptibilities, and further to attribute the production of symptoms to a relatively small fraction of the total dissolved nitrogen, the rate of elimination of which cannot be determined by direct measurement. Such an extension of effective nitrogen elimination constants far beyond the limits warranted by direct measurement was in fact made the basis of a suggested routine for the denitrogenation of aviators, with the additional assumption that "slow" nitrogen, once removed, would be reabsorbed equally slowly during the breathing of air prior to ascent (Bazett, Thompson and Bateman 1941, 1942). The procedure now appears to be warranted both by the original experimental data and that reviewed by Fraser, Stewart and Manning (1942), to which may perhaps be added recent results from the Yale laboratory (Fulton, 1944). We believe however that a direct proof of the importance of a "slow" nitrogen fraction has been lacking. The method of true equilibration of the body with known partial pressures of nitrogen, used in the present series of experiments, permits, in principle, the measurement of the rate at which the "effective" or symptom-producing nitrogen can be eliminated, and hence the establishment of its relationship to the overall rates as usually measured. Our first exploratory application of the method fully justifies the "slow" nitrogen hypothesis for it shows conclusively that if the time of half-saturation for the "effective" nitrogen is around 100 minutes for the three relatively insusceptible subjects, it must be at least 260 minutes for the fourth and most susceptible; if the six hour period was not sufficient for virtually complete equilibration of the former group, then both of these half-desaturation times will have to be increased; in any event they cannot be smaller than the values given. This brings at least one figure far outside the range of directly measured values.

In view of the apparent importance of a slow desaturation process that cannot be detected by the usual methods of measurement, it is of interest that signs have been observed of a correlation between susceptibility to decompression sickness and measured rates of inert gas exchange (Wu, 1942; H. B. Jones et al, 1942; Stevens et al, 1943). The correlation is not particularly striking, but insofar as it is genuine it must imply the existence of a relationship between the various desaturation constants of the body. Such a relationship would be expected if differences in gross circulation rate are responsible for variations in susceptibility among individuals, but it would be hard to explain if susceptible persons owed their condition to local and perhaps pathological states unrelated to the efficiency of their general circulation. The question evidently merits further experimental study.

REFERENCES

Bazett, H.C., Thompson, J.W. and Bateman, J.B. 1941. Report to National Research Council, Canada, November 1941.

Bazett, H.C., Thompson, J.W. and Bateman, J.B. 1942. Proc. 15th Meeting of Associate Committee on Aviation Medical Research, National Research Council, Canada, June 1942.

Behnke, A.R. and Willmon, T.L. 1941. Am. J. Physiol., 131, 619-626.

Behnke, A.R., Welham, W. and Yarbrough, O.D. 1942. O.S.R.D., C.A.M. Report No. 114, 15 December 1942.

Boothby, W.M. 1944, Handbook (see below), Chart A-1, Table 1.

Boothby, W.M., Lovelace, W.R. and Benson, O.O. 1942. "Physiology of Flight," Aero Medical Research Laboratory, Experimental Engineering Section, Materiel Center, Wright Field, Dayton, Ohio. Fig. 15, page 27.

Code, C.F. and Robinson, F.J. 1944. Subcommittee on Decompression Sickness, Minutes, 8 February 1944.

Ferris, E.B., Webb, J.P., Ryder, H.W., Engel, G.L., Romano, J. and Blankenhorn, M.S. 1943. O.S.R.D., C.A.M. Report No. 121, 16 February 1943.

Fraser, A.M., Stewart, C.B. and Manning, G.W. 1942. Report for Associate Committee on Aviation Medical Research, National Research Council, Canada, 17 Sept. 1942.

Fulton, J.F. 1944. O.S.R.D., Committee on Medical Research, Bi-monthly Progress Report No. 18 on Contract CEMomr-38, 1 June 1944.

Handbook of Respiratory Data in Aviation, 1944. Subcommittee on Oxygen and Anoxia, National Research Council, Washington, D. C.

Jones, H.B., Smith, R., Sears, N., Wu, C., Larkin, J., French, R., Hamilton, J. and Lawrence, J.H. 1942. O.S.R.D., C.A.M. Report No. 51, 29 May 1942.

Stevens, C.D., Ryder, H.W., Ferris, E.B., Engel, G.L., Webb, J.P., Senior, F. and Friedlander, J.K. 1943. O.S.R.D., C.A.M. Report No. 237, December 1943.

Wu, C. 1942. O.S.R.D., C.A.M. Report No. 52, 29 May 1942.

Yale Aero Medical Unit, 1944. Private communication from Dr. Nims.

Table 1

DESCRIPTION OF SUBJECTS

	R.S.	L.C.	R.H.	J.B.
Sex	F	F	F	M
Age	38	37	19	36
Height, cm.	157	158	160	173
Weight, kg.	65.5	72	47	66.2

Table 2

DEGREES OF IMMUNITY TO DECOMPRESSION SICKNESS FOLLOWING VARIOUS FORMS OF DESATURATION

Columns (3), (4) and (5) give details of gas inhaled, duration and altitude prior to decompression.
Columns (6) to (9) give scores (see text) obtained by four subjects during a 90-minute flight, with exercise, at 35,000 feet.

		Procedure before Decompression			Scores at 35,000 Feet			
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
No.	Date	% O_2 inhaled	Duration (minutes)	Altitude (feet)	R.S.	L.C.	R.H.	J.B.
1	18 Feb.	(20.9)	-	Ground	63	50	86	62
7	23 Mar.	(20.9)	-	"	147	64	121	68
2	22 Feb.	100	50	"	84+	107	120+	71
5	15 Mar.	100	50	"	297	162	360+	121
3	6 Mar.	100	80	"	170+	284	(44)	111
4	10 Mar.	100	110	"	327	360++	196	144
6	20 Mar.	100	110	"	360+	360+	350+	101
10	5 May	100	240	"	--	--	--	265
12	22 May	100	315	"	--	--	--	277
14	31 May	100	390	"	--	--	--	360++
8	10 Apr.	40	360	15,000	360+	360+	344+	98
9	3 May	40	360	15,000	319+	360+	360+	131
16	31 Aug.	30	360	15,000	--	348	--	106
11	11 May	40	360	Ground	143(+)	156	171	90
13	25 May	57	360	"	137(+)	351	335	167
15	28 Aug.	40	720	Ground	--	--	--	113
17	2 Sept.	59	720	"	--	--	--	271

Table 3

VALUE OF SIX HOURS AT 15,000 FEET BREATHING 30% AND 40% OXYGEN, EXPRESSED IN TERMS OF THE DURATION OF EXPOSURE TO PURE OXYGEN AT GROUND LEVEL REQUIRED TO GIVE THE SAME DEGREE OF IMMUNITY

Per cent oxygen	Subject	Mean score	Mean score without denitrogenation	Equivalent time, minutes
40	R.S.	340+	102	109+
	L.C.	360+	55	104+
	R.H.	350+	100+	(94)
	J.B.	115	65	89
30	L.C.	348	55	98
	J.B.	106	65	81

Table 4

VALUE OF SIX HOURS INHALATION OF 40% AND 57% OXYGEN AT GROUND LEVEL, EXPRESSED IN TERMS OF THE DURATION OF EXPOSURE TO PURE OXYGEN AT GROUND LEVEL REQUIRED TO GIVE THE SAME DEGREE OF IMMUNITY

Experiment	Per cent oxygen	Subject	Score	Equivalent time, (min.)
11	40	R.S.	143(+)	29(+)
		L.C.	156	54
		R.H.	171	(41)
		J.B.	90	53
13	57	R.S.	137(++)	25(++)
		L.C.	351	99
		R.H.	335	(89)
		J.B.	167	157

Table 5

CALCULATION OF ELIMINATION RATES OF SYMPTOM-PRODUCING NITROGEN

Column (4) gives alveolar nitrogen pressures during inhalation of nitrogen + oxygen mixtures containing oxygen fractions given in Column (2). When such mixtures have been inhaled for sufficiently long periods of time, the fractions of normal dissolved nitrogen remaining in the body are those given in Column (5). Subjects in this condition show the same degree of immunity to decompression sickness as they do after inhaling pure oxygen at ground level for the periods given in Column (6). These data are plotted in Fig. 4.

(1)	(2)	(3)	(4)	(5)	(6)			
Exp. No.	fO	Altitude (feet)	pN''	pN''/594	Equivalent times on pure oxygen (minutes)			
					R.S.	L.C.	R.H.	J.B.
8	0.405	15,000	233.0	0.392	117+	104+	60-123	--
9	0.399	15,000	233.3	0.393	101	104+	62-130	--
16	0.298	15,000	272.3	0.459	--	98	--	--
11	0.398	1,000	419.6	0.706	29+	54	29-54	--
15	"	"	"	"	--	--	--	94
13	0.577	1,000	290.2	0.489	25(++)	99	59-120	--
17	0.585	"	285.0	0.480	--	--	--	271

Table 6

CALCULATION OF DISSOLVED NITROGEN FRACTION REMAINING AFTER SIX HOURS INHALATION OF VARIOUS NITROGEN-OXYGEN MIXTURES IN THE CASE OF A SUBJECT FOR WHOM SIX HOURS IS INSUFFICIENT FOR COMPLETE EQUILIBRATION WITH THE INHALED PARTIAL PRESSURE OF NITROGEN.

Assumptions are discussed in text.

The data in Column (7) are plotted in Fig. 4.

Subject: J.B.

(1)	(2)	(3)	(4)	(5)	(6)	(7)
Exp. No.	fO	Altitude	N_2 fraction left at equilibrium (from Table 5)	N_2 fraction left after six hours (from Col. (4))	Score	Equivalent time on pure O_2 (minutes)
8	0.405	15,000	0.392	0.635	98	67
9	0.399	15,000	0.393	0.635	131	112
16	0.298	15,000	0.459	0.675	106	81
11	0.398	1,000	0.706	0.824	90	53
13	0.577	1,000	0.489	0.693	167	157

LEGENDS TO FIGURES

Fig. 1: Data illustrating the degrees of immunity to decompression sickness acquired by four persons after breathing pure oxygen for various periods.
Abscissa: duration of oxygen breathing.
Ordinate: degree of immunity, or recorded score in standard flight with exercise at 35,000 feet.
The highest possible recorded score is 360 for a stay of 90 minutes at 35,000 feet without symptoms. The true score in such a case must be greater than 360. Arrows are used in the diagram to indicate this.

Fig. 2: Indicating scores obtained by prolonged breathing of certain mixtures of nitrogen and oxygen, and the length of time for which pure oxygen must be breathed in order to obtain the same score.
Abscissa: logarithm of duration of oxygen breathing.
Ordinate: recorded score in standard flight, with exercise, at 35,000 feet.
Smooth curves based on data given in Table 2 and Fig. 1. Horizontal lines indicate scores obtained in six-hour and twelve-hour experiments with 40% and 60% oxygen. The abscissae of their intersections with the smooth curves give the equivalent period of oxygen breathing at ground level.

Fig. 3: Decompression sickness scores obtained by four subjects after "equilibration" with various mixtures of nitrogen and oxygen.
Abscissa: fraction of total dissolved nitrogen remaining in body after equilibrium level is reached.
Ordinate: score obtained in 90 minute flight, with exercise, at 35,000 feet.
"Equilibration" periods were six hours for subjects R.S., L.C., R.H. and twelve hours for J.B.

Fig. 4: Illustrating principle of method for determining elimination rate of symptom-producing nitrogen by measuring susceptibility at a known "equilibrium" level of dissolved nitrogen.
Abscissa: duration of inhalation of gas mixture, arbitrary unit.
Ordinate: fraction of symptom-producing nitrogen remaining in body.
Curve marked "oxygen + nitrogen" represents course of nitrogen elimination when a particular mixture is inhaled.
Curve marked "oxygen" represents nitrogen elimination when pure oxygen is inhaled. Both curves are exponentials with the same half-saturation time.
Horizontal dotted line represents the equilibrium level after prolonged inhalation of the nitrogen-oxygen mixture. The abscissa of its point of intersections with the "oxygen" curve gives the equivalent period of inhalation of pure oxygen. Inhalation of oxygen for this length of time will give the same protection against decompression sickness as prolonged inhalation of the nitrogen-oxygen mixture. Clearly the course of the oxygen curve, which in general is unknown, can be plotted experimentally by comparing "equilibrium" scores, obtained with mixtures containing various proportions of nitrogen and oxygen, with scores obtained after inhaling pure oxygen for various periods.

Legends to Figures (cont.)

Fig. 5: Elimination rates of symptom-producing nitrogen.
Abscissa: duration of oxygen breathing at ground level.
Ordinate: fraction of initial dissolved nitrogen remaining after desaturation.
Points are based entirely upon measurement of susceptibility to decompression sickness. They show the fractions of symptom-producing nitrogen remaining in the body after pure oxygen has been breathed for various periods, the latter values having been obtained from "equilibration" data in the manner indicated in Fig. 2 and Fig. 3.

Smooth curves are measured nitrogen elimination curves obtained by Behnke and Willmon, 1941 (lower curve) and Boothby, Lovelace and Benson, 1942 (upper curve).

Broken curve is drawn through the experimental points for the most susceptible subject. It indicates a half-desaturation time of 270 minutes for the symptom-producing nitrogen of this subject, compared with the values 60-90 minutes indicated by the smooth curve.

EFFECTS OF PREOXYGENATION

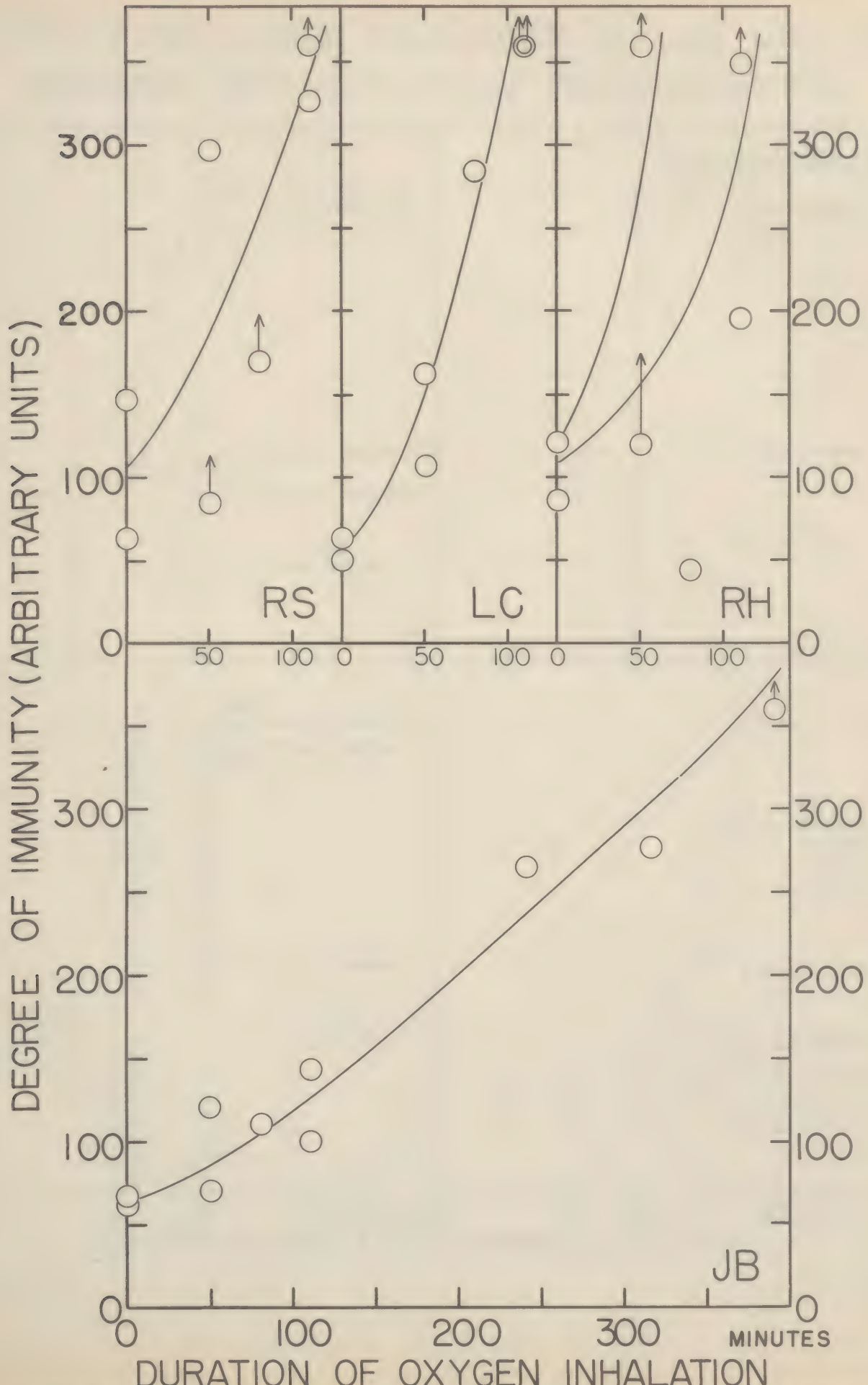
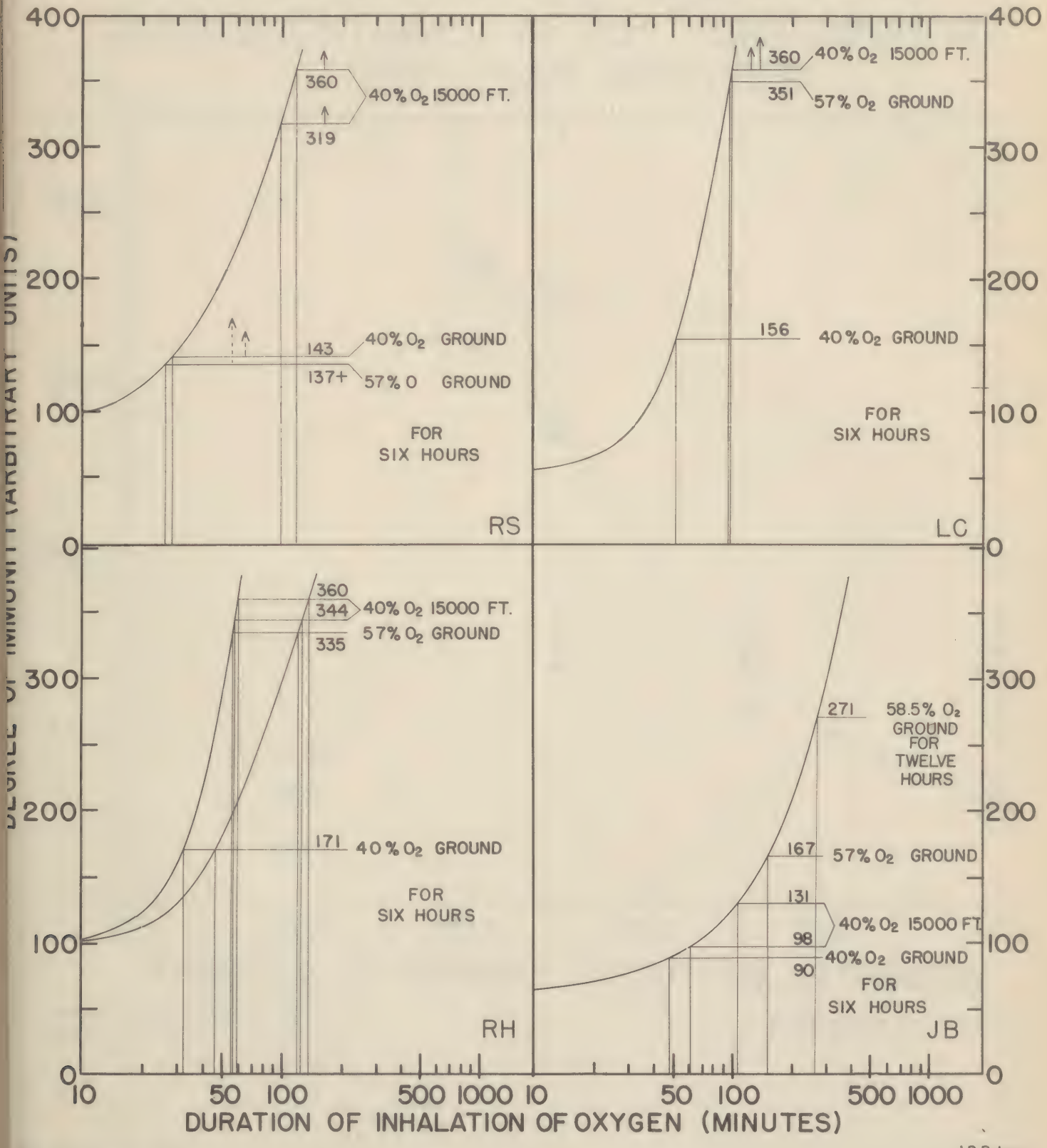


Chart No. VII – 8a Mayo Aero Medical Unit J.B. Bateman Aug. 1944

EFFECTS OF PROLONGED INHALATION OF GAS MIXTURES COMPARED WITH EFFECTS OF PREOXYGENATION



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J.B. Bateman
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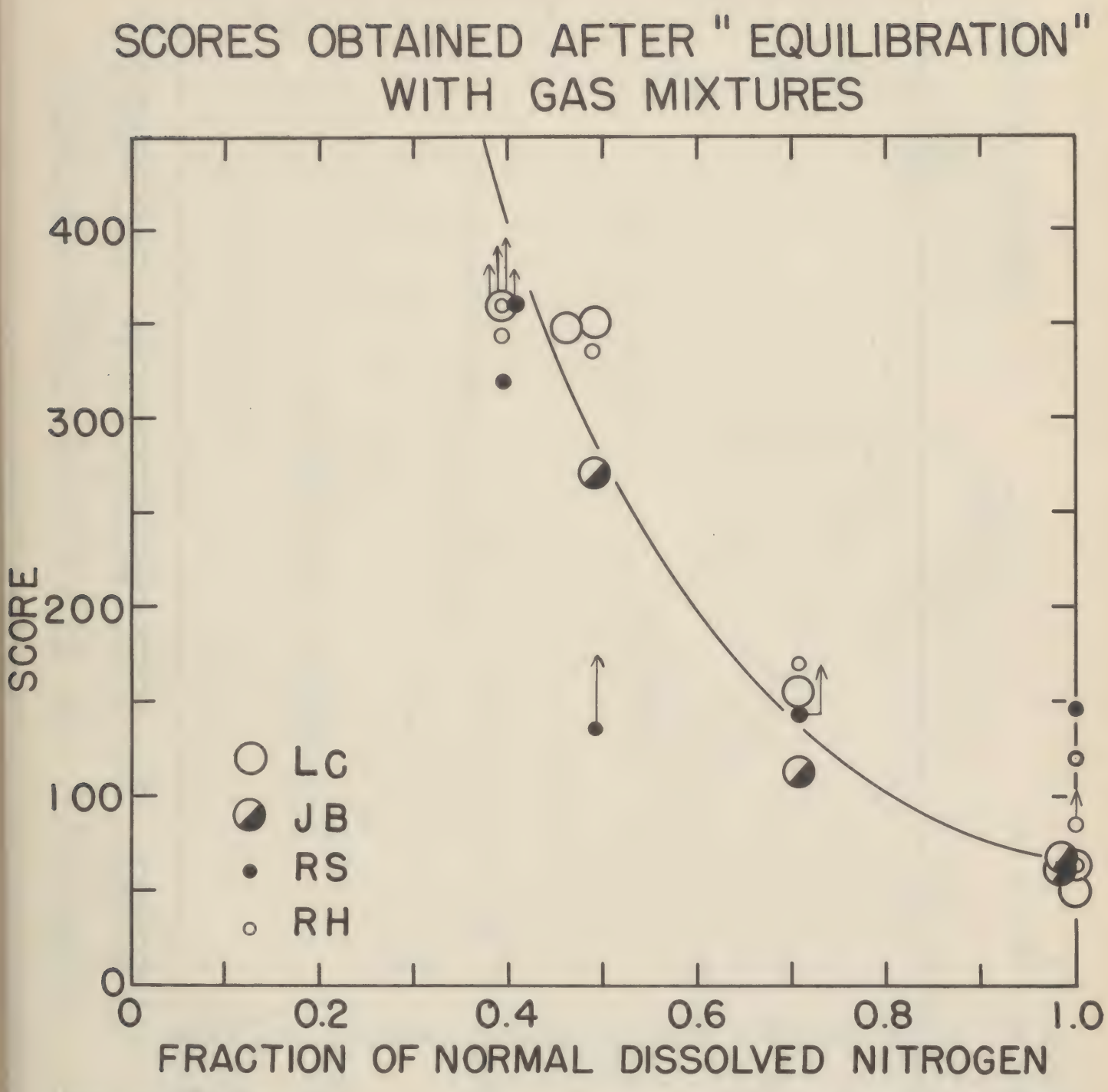

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Chart VII – 8 g

J.B. Bateman Aug. 1944

PRINCIPLE OF EQUILIBRATION METHOD IN STUDY OF DECOMPRESSION SICKNESS

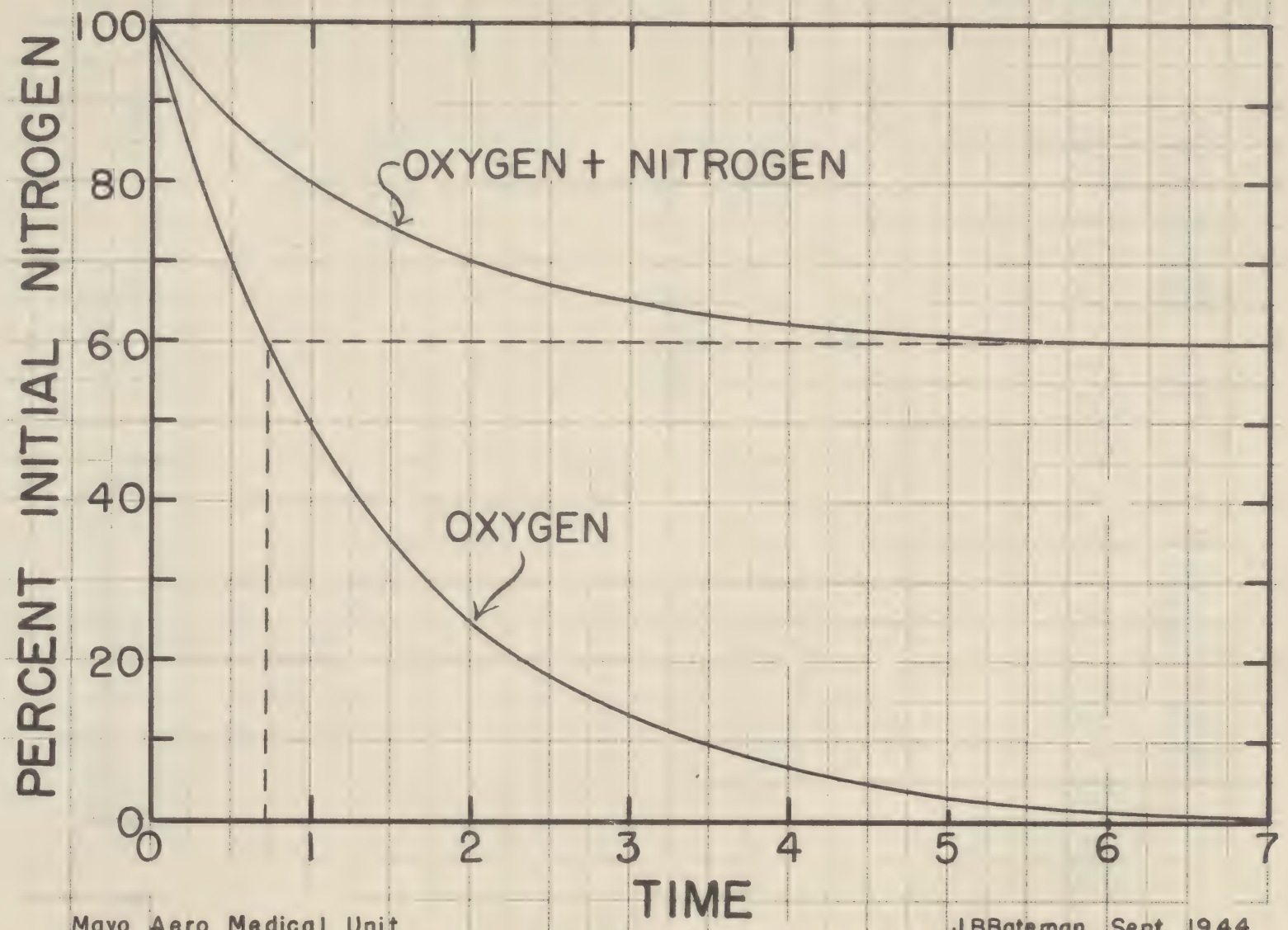

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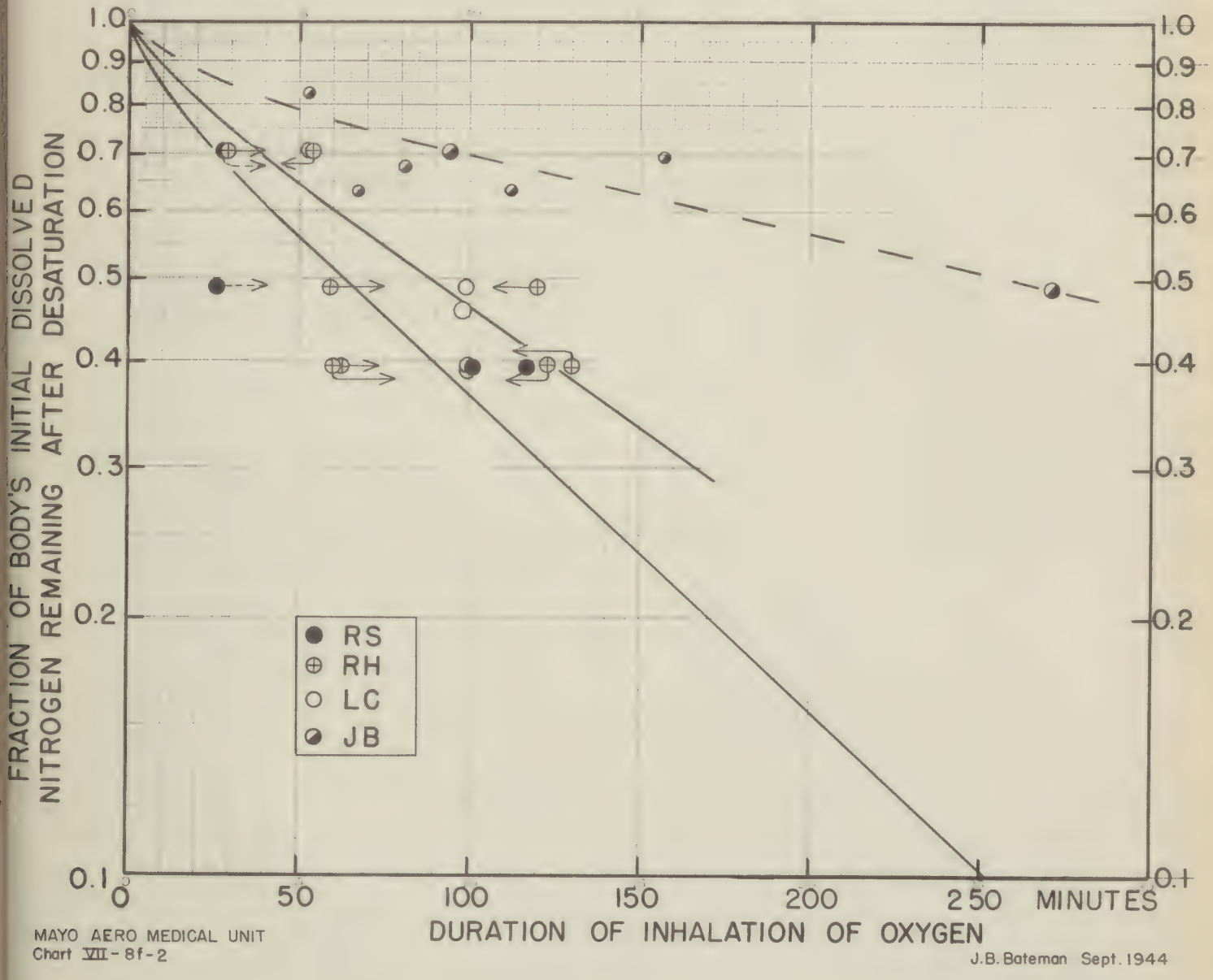
Chart VII 8 d

J.B.Bateman Sept. 1944

COURSE OF ELIMINATION OF SYMPTOM-PRODUCING NITROGEN



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J.B. Bateman Sept. 1944

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Report No. 381
September 1944

THE REDUCTION OF ALVEOLAR CARBON DIOXIDE PRESSURE DURING PRESSURE BREATHING AND ITS RELATION TO HYPERVENTILATION, TOGETHER WITH A NEW METHOD OF REPRESENTING THE EFFECTS OF HYPERVENTILATION. By J. B. Bateman, Mayo Aero Medical Unit, Rochester, Minnesota.
Responsible Investigator: Walter M. Boothby. (O.S.R.D. contract: OEMcmr-129)

ABSTRACT

The development of decreased alveolar carbon dioxide pressures during pressure breathing at ground level and the subsequent return to normal values occur significantly more rapidly than in the case of voluntary hyperventilation.

This experimental fact is discussed with the aid of new diagrams, based on the blood nomogram, showing the relation between ventilation rate, alveolar carbon dioxide pressure, and venous carbon dioxide pressure. The facts concerning the kinetics of ordinary hyperventilation are accounted for fairly satisfactorily by such considerations. The contrasting behavior of the alveolar carbon dioxide pressure in pressure breathing leads us to conclude that in this case additional factors are involved, including possible decrease in cardiac minute volume, decrease in peripheral circulation rate and expulsion of blood from the lung during pressure breathing, with a reflex compensatory diminution of ventilation rate after return to normal intrapulmonary pressure. It is therefore possible that the decreased alveolar carbon dioxide pressures are not exclusively due to an increased ventilation rate associated with pressure breathing, and are hence not entirely reliable as an index of developing acapnia.

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INTRODUCTION

1. Pressure breathing at ground level with constant pressure without the aid of a pressure vest has been found to be accompanied by a decrease of 4 to 8 mm. Hg in the alveolar carbon dioxide pressures of several trained and experienced subjects studied in this laboratory. This decrease is of appreciable duration; it can still be observed after five minutes of pressure breathing. Although in several other subjects, on the contrary, the initial rapid decrease proved to be succeeded by a rapid return to normal values (compare ref. (4)), the nature of the more persistent effect in the former group was worth examining. When the experiments were begun it was believed to be an experimental arifact associated with imperfect mixing in the lungs (compare ref. (1)), and it seemed appropriate to test this possibility by comparing the rate at which the normal alveolar carbon dioxide level is regained, after return to zero pressure, with rates of recovery from voluntary hyperventilation. We have in the meantime ceased to take the artifact hypothesis at all seriously in the present context. However, our results and their analysis may be applicable to current discussions of hyperventilation and pressure breathing. They have already been referred to by ourselves and by others, in discussions and reports unconnected with this laboratory.

METHODS

Pressure breathing: Oxygen. Bendix pressure demand regulator set at 8 inches of water. Bulbulian Type 21B pressure mask provided with T-piece below mask for collection of alveolar samples. Pressure always released during alveolar expiration. Collection of samples through T-piece gave the same results as removing mask and using standard mouthpiece.

Hyperventilation: "Moderate" hyperventilation is deep inspiration and normal expiration five times per minute. "Severe" hyperventilation is deep inspiration and deep expiration ten times per minute.

1. Course of change of alveolar carbon dioxide pressure, pC'', during pressure breathing and hyperventilation: The results of several individual runs on one subject are shown in Fig. 1, which gives some idea of the reproducibility of the data. One notes the following tendencies:

(a) During pressure breathing an initial sharp decrease of pC'' of about 6 mm. Hg, which may be followed by a certain amount of recovery.

(b) A much slower decrease during "moderate" hyperventilation, arriving after 5 minutes at a level, about 7 mm. Hg. below normal, not greatly different from that resulting from 5 minutes pressure breathing.

(c) During "severe" hyperventilation, a sharp initial decrease of 8-11 mm. Hg. followed by a further slow decrease, reaching a value of 13-14 mm. Hg. below normal in 5 minutes.

These differences become more clear-cut when the changes in pC'' are expressed as percentages of the change observed after five minutes and the individual values then averaged for all three subjects (Fig. 2). We note that the very rapid inital decrease is common to both pressure breathing and "severe" hyperventilation but is not observed with "moderate" hyperventilation.

2. Course of recovery from the effects of pressure breathing and hyperventilation: In Fig. 3 the gain in pC'' during recovery is expressed as percentage of the preceding decrease. We note that

(a) Recovery from two deep breaths and from two breaths of pressure breathing occurs very rapidly. It is complete in less than one minute.

(b) Recovery from five minutes pressure breathing is just as rapid as recovery from two breaths pressure breathing or from two deep breaths.

(c) Recovery from "moderate" hyperventilation requires four or five minutes, despite the fact that the actual decrease in pC'' resulting from this procedure is no greater than that resulting from pressure breathing.

(d) Recovery from "severe" hyperventilation follows at first the same course as recovery from "moderate" hyperventilation. The curves then diverge, the later stages of recovery from "severe" hyperventilation becoming gradually slower.

The contrast between true hyperventilation and pressure breathing is brought out in Fig. 4, in which the times of half recovery, taken from Fig. 3, are plotted against the maximum decreases in pC''. This method of presentation brings out the main point, but it is of course deceptive, in that it fails to show the differences between "moderate" and "severe" hyperventilation arising from the differences in the curves during the second half of the recovery process.

DISCUSSION

How can these rather striking kinetic differences be accounted for? First we can draw an obvious distinction between processes involving only the arterial blood and processes involving the tissues. A decrease in pC'' at constant venous carbon dioxide pressure has the property that it is rapid in onset (time considerably less than circulation time) and is transitory. The observed effect of two deep breaths provides an illustration: rapid decrease in pC'', rapid recovery. If perpetuated by continued hyperventilation or by other means, the decrease in pC'' must involve a decrease in venous carbon dioxide pressure. This, necessitating loss of some of the combined carbon dioxide in the tissues, occurs relatively slowly.

These processes may be followed more closely by reference to a diagram such as Fig. 5, in which alveolar carbon dioxide pressure is plotted against venous carbon dioxide pressure. The diagram refers to the case of a subject whose oxygen consumption, circulation rate, and metabolic respiratory quotient* (0.8) remain constant at all times, changes being brought about solely by changes in ventilation rate. Two sets of reference lines are included. Those for various values of the respiratory quotient* are implied in L. J. Henderson's nomograms representing the properties of human blood (7) and were derived from that source; those for various values of the alveolar ventilation rate were obtained by combining the same data with a formula derived by Chadwick, Otis, Rahn, Epstein and Fenn (5):

$$V = 0.864\ YQ/pC''$$

where

V = alveolar ventilation rate, liters per minute moist gas at 37° C.

Y = oxygen consumption = 300 cc./min., dry, at 0° C. and 760 mm.

In Fig. 5 a single transverse line, for a respiratory quotient 0.8, which is taken as the metabolic respiratory quotient, represents all theoretically possible steady states for a person subject to the limitations defined above. Of all these possible states, that which is actually found under normal conditions is given by the single point O. That it must be this point and not some other is of course determined by factors in physiological coordination for which no allowance has been made in current physico-chemical descriptions of blood. Starting from O as origin, d decreases in alveolar carbon dioxide pressure can result in several ways:

At the one extreme, a very slow progressive increase in ventilation rate could occur in such a way that the subject, although losing carbon dioxide and suffering a gradual decrease in venous carbon dioxide pressure, would always remain to all intents and purposes in a steady state. This change, which would appear on Fig. 5 as a downward movement from O along the reference line for Q = 0.8, may be described as hyperventilation without change in respiratory quotient. At the other

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* In this paper the term "respiratory quotient," for which the symbol Q is also used, is intended to specify the nature of the gas exchange occuring in the lungs at any time. Unless the subject happens to be in a "steady state," the respiratory quotient so defined will not be equal to the "combustion quotient" or the "metabolic respiratory quotient." Thus our definition represents an extension of the term which is usually employed in literature on metabolism to denote the combustion quotient. This suggestion is made only, we hope, as a temporary expedient in absence of an accepted consistent terminology.

extreme, a sudden increase in ventilation rate results in rapid decrease of pC'' without change in venous carbon dioxide pressure. The new instantaneous state is defined by a point lying on the appropriate reference line for alveolar ventilation rate and on the same horizontal level as O. If the increased ventilation is continued, the initial rapid change must be succeeded by a further slow decrease in pC'' and a simultaneous decrease in venous carbon dioxide pressure, the course of the change following the line of constant ventilation rate in the manner shown by the descending portions of the heavy lines C and A in Fig. 5. Since the reference lines for constant ventilation and constant respiratory quotient are not parallel, it is obvious that once the initial period of rapid adjustment is over, continued constant hyperventilation must be accompanied by a gradual decrease in respiratory quotient. There will be a trend, in other words, toward the original metabolic respiratory quotient. In general other factors will intervene before the change is completed, but it is possible in cases of mild hyperventilation that a new steady state may be attained in this manner and may be compatible with continued physical and mental well-being. To return to the subject of immediate interest, we may say that the type of change described above and indicated in curves A and C accounts fairly well for the facts observed in the cases of "moderate" and "severe" hyperventilation respectively. The increasing slope of the reference lines with increasing ventilation indicates the increasing relative importance of the initial rapid fall in pC'', which may perhaps be accentuated by the fact that in the "moderate" hyperventialtion procedure used in our experiments there was opportunity during the slow normal expirations for partial recovery of the decreased pC'' values during each breath. If this is correct, curve A should be replaced by a zig-zag. The case of pressure breathing, with an initial sharp decrease followed by a slow increase of pC'', is illustrated by curve B, which shows the effect of a decrease of ventilation rate in causing an increase of pC'' without however preventing continued loss of tissue carbon dioxide in excess of that corresponding to the metabolic respiratory quotient.

It remains to consider the recovery curves. For "moderate" and "severe" hyperventilation, the initial stages of recovery are presumably represented by the horizontal portions of A' and B'. These involve in each case roughly the same proportion of the total change in pC'', so that it is not surprising to find that the two recovery curves have an initial stage in common, nor that they later separate, in accordance with different absolute amounts of carbon dioxide that have to be reaccumulated by the tissues. It is however surprising that the initial stage, although still comparable with the circulation time, is so much slower than the corresponding process in the response to increased ventilation.* Contributing factors are undoubtedly the rate of transfer of carbon dioxide from blood to alveolar air, which delays the establishment of an increased pC'' after return to a normal ventilation rate, and also the convergence of the ventilation lines with decreasing venous carbon dioxide pressure, which considerably enhances the relative importance of the "slow" recovery phase. Possibly other factors should also be considered.

The recovery curves for pressure breathing require some additional postulate. In the first place, it is not possible within the framework of the present assumptions to account for the persistent fall in pC'' during pressure breathing without admitting

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* A closely similar recovery curve following two minutes forced breathing is to be found in an early paper by Boothby (3).

that there must be some fall in venous carbon dioxide pressure. How then can recovery be so much more rapid than recovery from ordinary hyperventilation? The curves B' and B'' suggest that this may result from a temporary decrease of ventilation, of reflex origin, following the period of pressure breathing. It must be remembered, however, that other relevant changes have been supposed to occur during pressure breathing, so that Fig. 5 may not be applicable to this case. There may sometimes be a decrease in cardiac output (2) (4) (6) (8) together with decreased peripheral circulation (2) (4) (6) and expulsion of stored blood from the lungs (4). Fig. 6 is meant to illustrate how a sudden decrease in cardiac minute volume could contribute both to rapid decrease in pC'' when pressure breathing is started, and to rapid recovery; it further illustrates how readjustment to a new steady state can in such a case be effected rapidly and without any significant change in CO_2 balance. It may be noted in passing, however, that a 30 per cent decrease in cardiac minute volume results, even at ground level when oxygen is being breathed, in a considerable and probably dangerous fall in venous oxygen pressure, and that this condition would not be significantly alleviated even if the response to decreased cardiac output were to follow the alternative but improbable course indicated by the vertical arrows in Fig. 6.

Expulsion of stored blood from the lung, and its storage elsewhere, could also contribute to a rapid recovery of pC'' if relatively venous stored blood were suddenly thrown back into the pulmonary circulation upon release of the raised intrapulmonary pressure. Decreased peripheral circulation during pressure breathing if accompanied by an increase in the volume of blood in the limbs, could act in the same manner.

Thus it appears probable that while the facts concerning the rates of decrease and increase of pC'' during and after ordinary hyperventilation can be broadly accounted for without postulating any physiological mechanism other than that arising directly from the altered ventilation rate, this is probably not true of the decreased pC'' accompanying pressure breathing. The exceptional rapidity with which the original pC'' is regained after pressure breathing shows that other changes are operative, among which may be a reflex (?) decrease in ventilation rate after a period of pressure breathing, decrease in cardiac minute volume, and sudden return of stored blood to the lungs. Insofar as a decrease in cardiac minute volume can be held responsible, it is probable that the decreased pC'' in pressure breathing is not a reliable index of significant loss of carbon dioxide - cannot, in other words, be regarded as a valid criterion of acapnia.

REFERENCES

(1) Bateman, J.B. and Boothby, W.M. 1944. O.S.R.D., C.A.M. Report No. 341.

(2) Bloom, W.L., Kaufman, S.S., Nims, L.F. and Nyboer, J. 1944. O.S.R.D., C.A.M. Report No. 246.

(3) Boothby, W.M. 1912. J. Physiol., 45, 328.

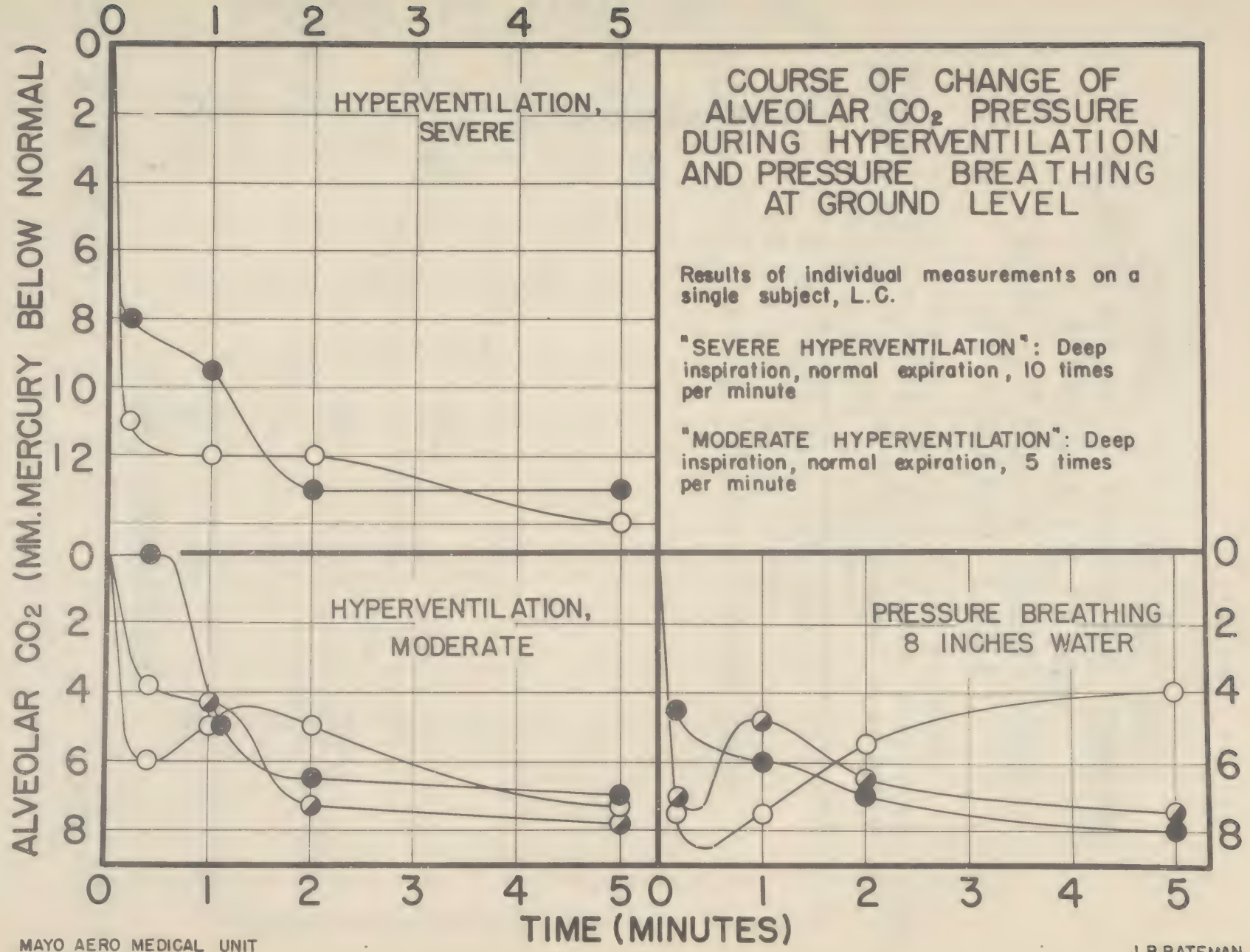
(4) Chadwick, L.E., Fenn, W.O., Otis, A.B. and Rahn, H. 1943. O.S.R.D. Second report on Contract OEMcmr-147; summary in C.A.M. Report No. 249.

(5) Chadwick, L.E., Otis, A.B., Rahn, H., Epstein, M.A. and Fenn, W.O. 1944. O.S.R.D., C.A.M. Report No. 304.

(6) Fenn, W.O., Chadwick, L.E., Mullins, L.J., Dern, R.J., Otis, A.B., Blair, H.A., Rahn, H. and Gesselin, R.E. 1943. O.S.R.D., C.A.M. Report No. 111.

(7) Hendersen, L.J. 1928. Blood. A study in general physiology. Yale University Press.

(8) Starr, I. and McMichael, M. 1943. O.S.R.D., C.A.M. Report No. 165.



MAYO AERO MEDICAL UNIT
CHART NO. XIX - 4 (1)

J.B.BATEMAN
SEPT. 1944

COURSE OF CHANGE OF ALVEOLAR CO_2 PRESSURE DURING HYPERVENTILATION AND PRESSURE BREATHING AT GROUND LEVEL

Average of all data for 3 subjects

Abscissa: Time in minutes at which alveolar samples were taken

Ordinate: Change of alveolar CO_2 expressed as percentage of change produced in 5 minutes

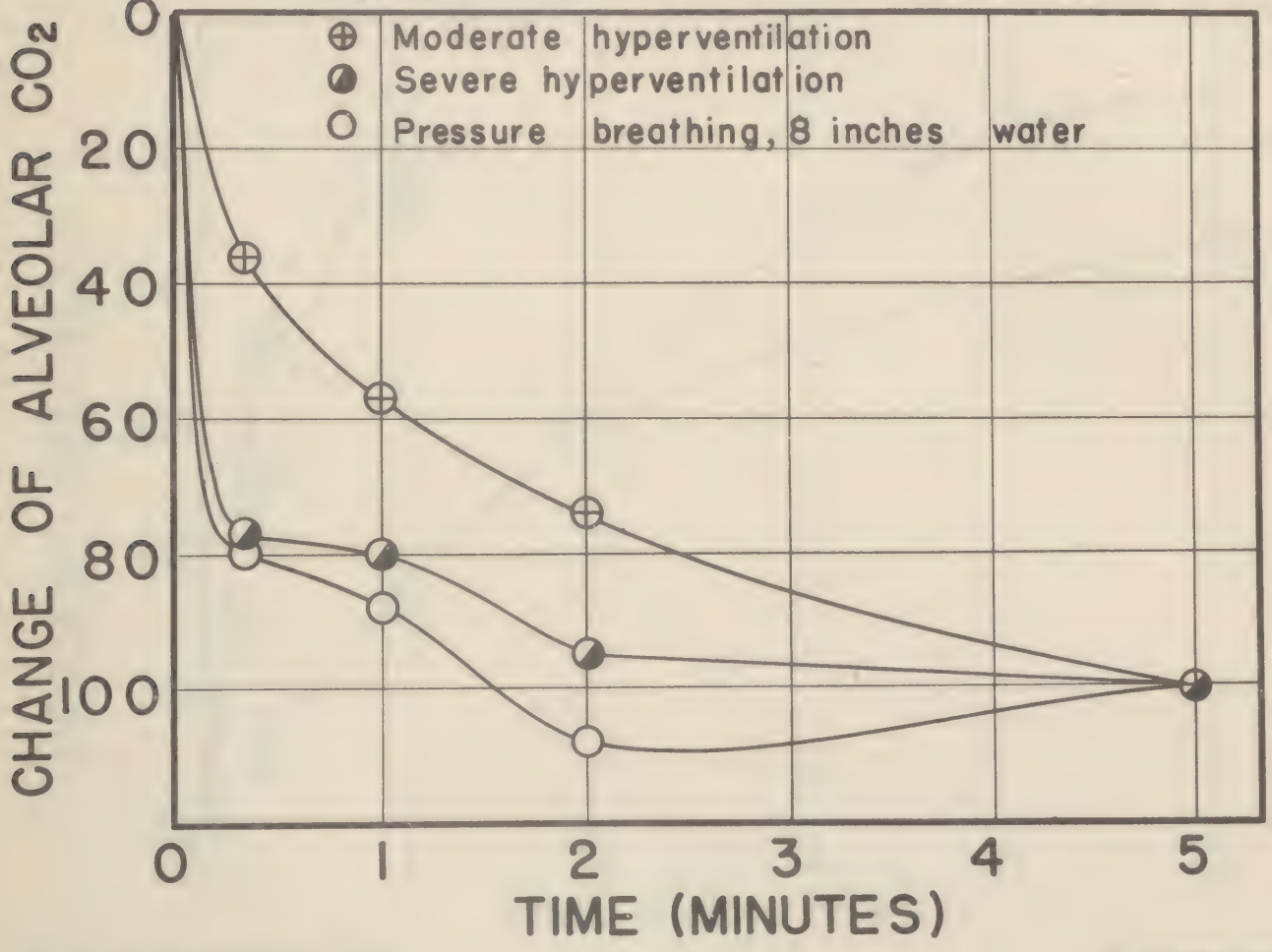


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CHART NO. XIX - 4 (2)

J. B. BATEMAN
SEPT. 1944

RETURN OF ALVEOLAR CO_2 TO NORMAL VALUE FOLLOWING HYPERVENTILATION AND PRESSURE BREATHING AT GROUND LEVEL

○ After 2 breaths pressure breathing, 8 inches water
● After 2 deep breaths
◐ After 5 minutes pressure breathing, 8 inches water
⊕ After 5 minutes moderate hyperventilation: Deep inspiration normal expiration, 5 times per minute
⊗ After 5 minutes hyperventilation: Deep inspiration, deep expiration, 10 times per minute

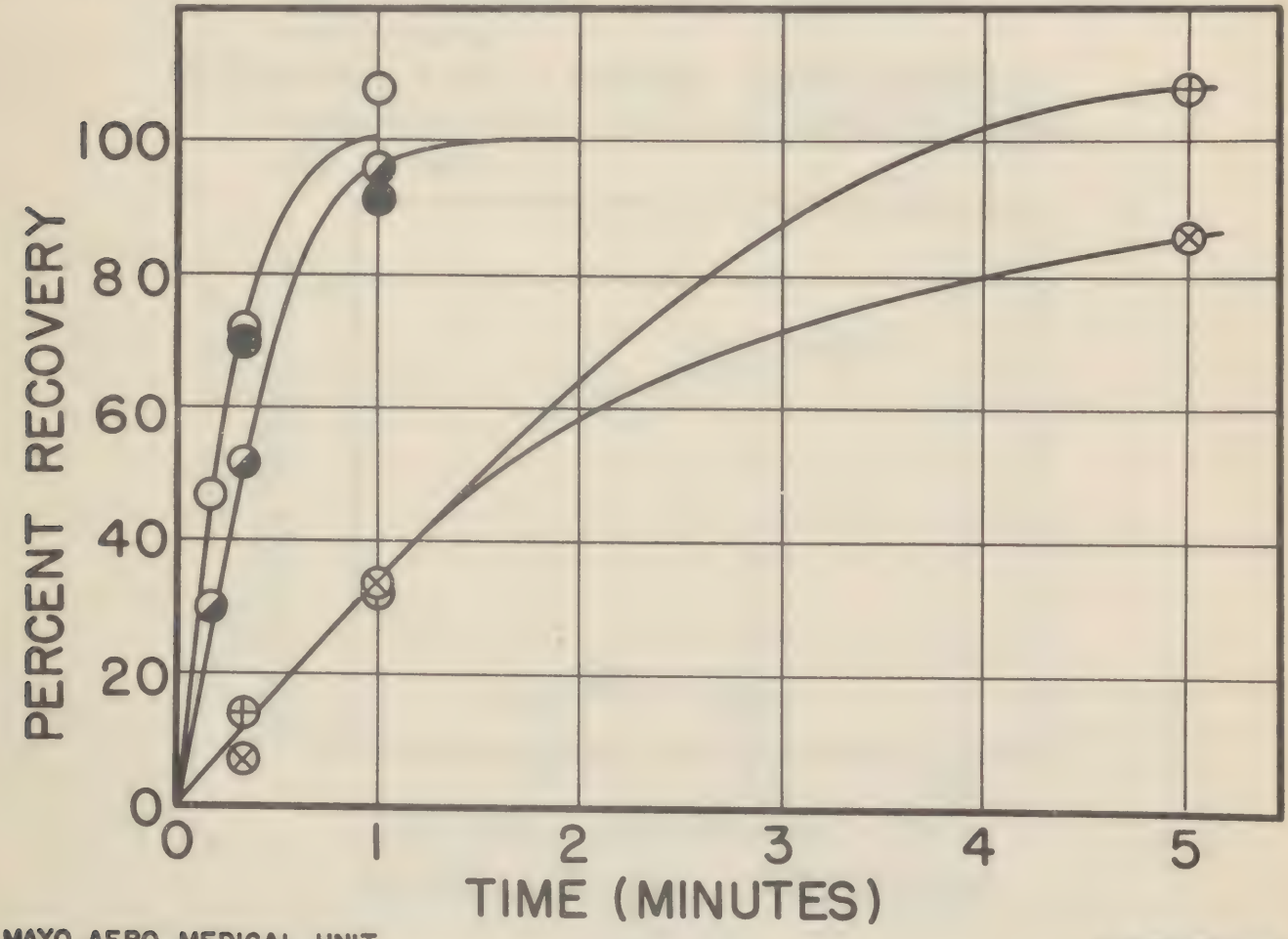

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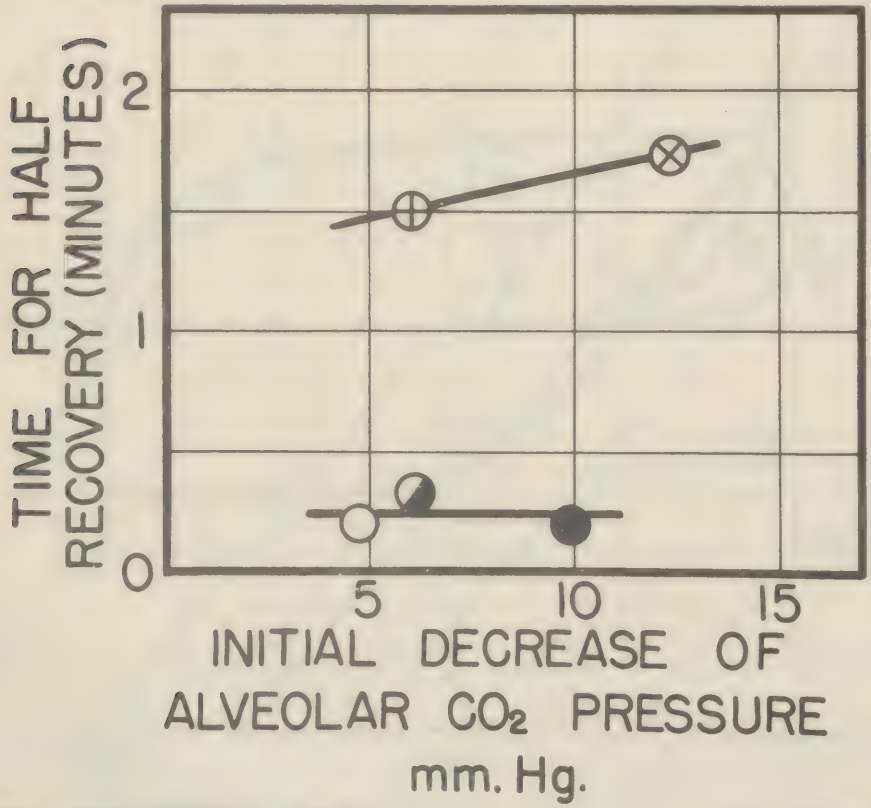
CHART NO. XXX - 4 (3)

J.B. BATEMAN
SEPT. 1944

TIMES FOR HALF RECOVERY FROM DECREASE IN ALVEOLAR CO_2 PRESSURE PRODUCED BY HYPERVENTILATION AND PRESSURE BREATHING AT GROUND LEVEL

- ● Recovery from 2 deep breaths
- ○ Recovery from 2 breaths of pressure breathing (8 inches water)
- ◒ Recovery from 5 minutes pressure breathing
- ⊕ Recovery from 5 minutes hyperventilation: deep inspiration, normal inspiration, 5 times per minute
- ⊗ Recovery from 5 minutes hyperventilation: deep inspiration, deep expiration, 10 times per minute



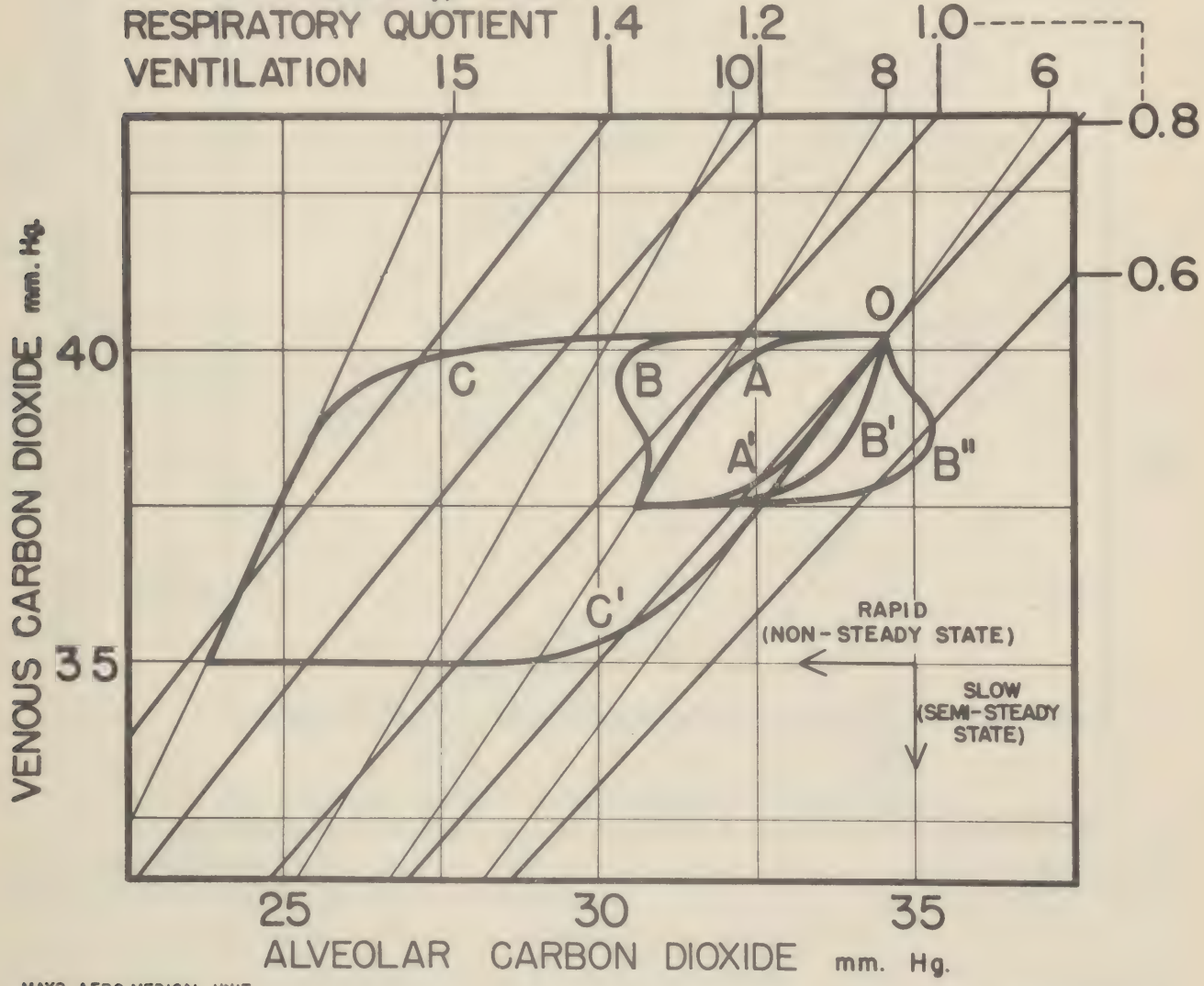
MAYO AERO MEDICAL UNIT
CHART NO. XIX-4(4)

J.B. BATEMAN
SEPT. 1944

CORRELATION OF CHANGES IN ALVEOLAR (ARTERIAL) AND VENOUS CARBON DIOXIDE PRESSURES DURING AND AFTER RECOVERY FROM HYPERVENTILATION

Heavy transverse lines are lines of equal respiratory quotient
Light transverse lines are lines of equal alveolar ventilation
Areas enclosed by heaviest lines represent course of change accompanying a period of hyperventilation followed by recovery, the normal state being represented by point O

AA' : very moderate hyperventilation
BB', BB" : suggested changes during and after pressure breathing
CC' : severe hyperventilation



MAYO AERO MEDICAL UNIT
CHART NO. XIX - 4 (5)

J.B. BATEMAN
SEPT. 1944

POSSIBLE CHANGES IN ALVEOLAR AND VENOUS CARBON DIOXIDE AND VENOUS OXYGEN PRESSURES FOLLOWING A DECREASE IN CARDIAC MINUTE VOLUME

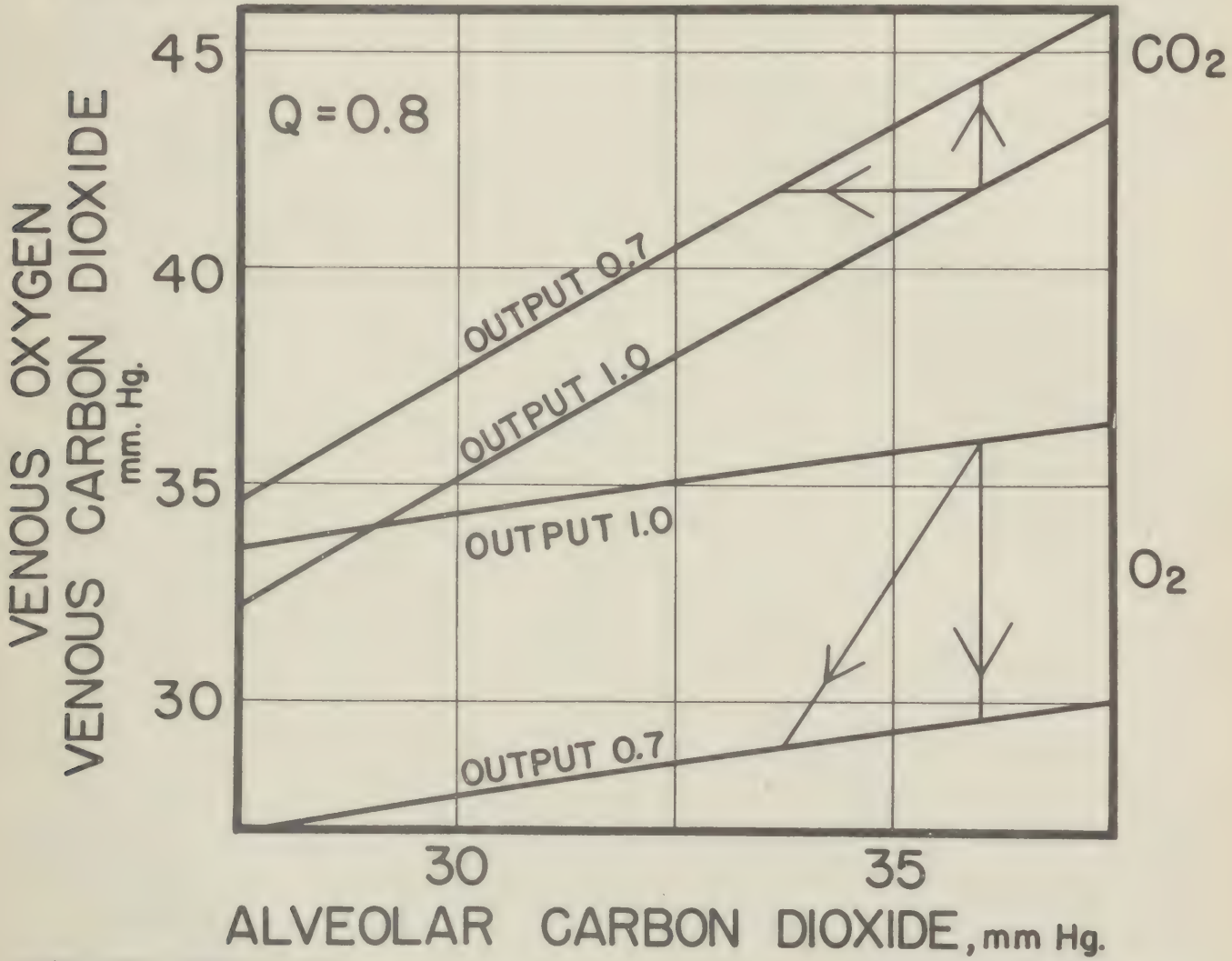


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CHART NO. XIX - 4(6)

J. B. BATEMAN
SEPT. 1944

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Report No. 428
OPEN May 2, 1945

THE EFFECT OF PRESSURE BREATHING UPON THE SKIN TEMPERATURES OF THE EXTREMITIES.
By J. B. Bateman and Charles Sheard, Mayo Aero Medical Unit, Rochester, Minnesota. (OSRD Contract: OEMcmr-129)

ABSTRACT

The present studies of the variations in skin temperature of the extremities resulting from pressure breathing, both in psychrometric rooms and in the decompression chamber, have provided evidence in support of an initial peripheral vasoconstriction following inception of constant positive pressure breathing. This is usually transient, however, being succeeded by a slow rise in temperature which usually exceeds the initial decrease. When conscious respiratory effort is abolished, as by the use of the Burns pneumatic resuscitator, the secondary rise in temperature appears to be absent.

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CMEM May 2, 1945

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REPORT

Introduction

An increase in intrapulmonary pressure of about 15 mm. of mercury is well tolerated by the majority of healthy persons. This fact implies the successful adaptation of the circulation to an entirely new set of mechanical conditions. Since the increase in pressure, which must, to a considerable extent, be transmitted to the entire thoracic cavity, is of the same order of magnitude as the blood pressure, it is obvious that changes must occur in order that normal circulation can continue against an increased pulmonary resistance. The details of this circulatory adaptation are not fully understood*, but it is acknowledged that there must be a rise in both arterial and venous blood pressure, a rise in intra-auricular pressure and an engorgement of veins in the systemic circulation. The fact that no untoward effects result from pressure breathing is in itself a proof that, in spite of these altered mechanical conditions, cardiac output is more or less maintained. It appears probable from measurements of performance of one kind or another that, as far as the cerebral circulation is concerned, no redistribution of blood occurs. It is known, however, that a considerable amount of blood is passively displaced from the lung during pressure breathing and that this change compensates in part for the effects of venous congestion. A further adaptation would appear to consist in a redistribution of blood in the systemic circulation whereby the blood flow to the internal organs is maintained, despite a significant decrease in cardiac output, at the expense of blood flow to the extremities. Plethysmographic measurements of various kinds(2)(3)(4) appear to demonstrate this decrease in blood flow in the extremities during the first few minutes of pressure breathing. According to Fenn and his collaborators this effect is accompanied by a constriction of the peripheral arteries.

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*Reference may be made to the admirable review by Barach, Fenn, Ferris and Schmidt.(1)

The peripheral redistribution of blood apparently demonstrated in these measurements is not of any subjective significance under ordinary conditions, but it has been suggested [4] that under operational conditions vasoconstriction in the extremities might have deleterious effects upon the manual dexterity of aviators. Thus an effect which under laboratory conditions is comparatively slight might be of some importance in the field. It seemed important therefore to investigate as carefully as possible the vascular changes in the extremities which occur during pressure breathing. The present paper is the outcome of an attempt to do this by means of measurement of the skin temperature under carefully controlled conditions.

Methods

In the present work experiments were made both in a constant temperature room and also at simulated altitudes in a decompression chamber. The former series enabled us to establish the effects which occurred with some certainty, while the series in the decompression chamber, which were of necessity less satisfactory than those made in the constant temperature room were run in order to satisfy ourselves that the change in conditions did not fundamentally modify the observed reactions.

The first series referred to was carried out in psychromatic rooms at one of the hospitals in Rochester, Minnesota, which the temperature was maintained at any desired temperature with an accuracy of $\pm$ 0.3° C. within a range of 20° to 30° C., and the humidity at 40 per cent. A uniform procedure was adopted throughout the series. The subject arrived, without having breakfasted, at 8:30 a.m. and was then allowed to rest in bed, lightly covered but with the extremities exposed, for an initial period of vascular adaptation. During this period the surface thermocouples were placed in position — 3 on each hand and 3 on each foot — in the manner described in previous papers by Sheard and collaborators (*vide* article by Sheard[6]). The recording of skin temperatures was commenced and at the end of the introductory period, which was usually marked by an approach of the temperatures of the fingers and toes to their respective levels, the experiment proper could be started. The pressure breathing mask was placed in position and the subject was allowed to breathe a gas mixture supplied through a standard pressure breathing regulator set at zero or at a positive pressure of 1 inch of water. The gas was either pure oxygen or a mixture containing 20% oxygen and 80% nitrogen. In view of the fluctuations in pressure which occur during the use of these regulators at ground level a pressure setting of 1 inch of water corresponds roughly to breathing at ambient pressure. The zero setting, on the other hand, involves an appreciable amount of suction during inspiration, and is a source of some discomfort.

Since the adjustment of the mask frequently caused some vasomotor disturbance a considerable time usually was allowed before the commencement of pressure breathing, temperature measurements being taken at frequent intervals (at least every 10 minutes) during this period. When sufficient stability had been attained the regulator setting was changed in most cases to 8 inches water, and temperature measurements were continued at shorter intervals. Temperature measurements during pressure breathing were continued either until a satisfactory effect was established or until the discomfort of the subject necessitated an early conclusion. Then the pressure was turned off and whenever possible the temperature readings were continued for a further period of 30 or 40 minutes.

The procedure followed in the decompression chamber was essentially the same, with some modification necessitated by the marked decrease in temperature which invariable occurs during decompression. It is impossible to avoid such a decrease. It can be minimized by slow ascent and its effects upon the subject to some extent reduced by the use of blankets. However these procedures are never entirely satisfactory and only a certain proportion of experiments made in the decompression chamber can be considered at all successful.

The majority of experiments were made with 3 female subjects with long experience in pressure breathing. Occasional runs were also possible with other subjects.

Experimental results

In presenting the results of these experiments, it may be said at once that the effects of pressure breathing upon the skin temperatures of the extremities, although by no means negligible, are readily obscured in many subjects by the effects of accidental stimuli. The necessity for carefully controlled conditions and for complete tranquility throughout an experiment cannot be too heavily stressed. It was not uncommon with certain of our subjects to find comparatively violent reactions to the adjustment of the pressure breathing mask or merely to the announced intention of increasing the pressure. This extreme vasomotor sensitiveness was not connected with any inability to withstand pressure breathing; it was merely a disturbing factor which prevented the profitable use of such subjects in experiments of this kind. On the other hand, experiments also had to be abandoned on occasion when after a reasonable period of adjustment the subject had failed to reach a state of vasomotor reactivity, by reason of prolonged dilatation or excessive constriction of the peripheral blood vessels.

The data obtained are illustrated by means of a series of representative diagrams. In what we shall in the following discussion regard as typical behavior, because it is the one that we have observed most frequently, a steady increase in intra-pulmonary pressure at first brings about a slight decrease in skin temperature of the extremities. This is transient and is succeeded by a slow rise in temperature which as a rule exceeds the initial decrease so that the peripheral vessels become more dilated than they were in the control period at zero pressure. When the pressure is turned off there may or may not be a tendency for vasoconstriction to occur; in the majority of cases the dilatation brought about by pressure breathing persists.

This typical behavior is shown in Figure 1 where it will be noted that both fingers and toes respond in the manner described. Figure 2 illustrates a case in which the typical response is confined to the fingers, the toes remaining constricted and somewhat below room temperature throughout the experiment. It will be noted that the typical transient constriction followed by slow dilatation occurred in this experiment with each successive increase in intrapulmonary pressure and, further, that the return to ambient pressure caused a slight transient constriction. Figure 3 illustrates an experiment of similar nature on another subject in whom, however, a reflex dilatation of the toes followed the corresponding response of the fingers. Figure 4 represents a case in which the fingers were unable to respond because of their initial state of dilatation and in which, therefore, the entire observed effect occurred in the toes. Figure 5 represents one of the less usual experiments, entirely satisfactory from a technical point of view, but in which no

effect whatever was observed when the pressure was increased. This result was obtained with a subject in whom what we have described as the typical response has been repeatedly and consistently observed.

In Figures 6 and 7 two experiments in the decompression chamber are presented. It has been mentioned already that such experiments are commonly less satisfactory than those made in a constant temperature room, but it seemed necessary to know, first, whether an altitude of 40,000 feet, with the hazard of decompression sickness, would modify the result already obtained, and, secondly, whether anoxia would produce any significant effect. Figure 6 gives the best answer that we were able to obtain to the first question. It will be noted that despite the cooling of the decompression chamber during ascent, amounting to about 3° C., it was possible to keep the fingers and toes at a reasonably steady temperature, and that the effect of pressure breathing on the temperature of the toes exceeded by far any effects produced by other circumstances, resembling very closely the typical effect of transient constriction followed by dilatation. The same can be said of the experiment reported in Figure 7, in which the anoxia produced by breathing 18 per cent oxygen at 11,000 feet was a significant factor. Here again, although throughout the experimental period the arterial saturation was not much greater than 75 per cent, the behavior of the finger temperatures was fairly typical.

We have not attempted in this investigation to study, in any detail the effects of intermittent pressure breathing, involving, as they do, such secondary factors as hyperventilation, but two experiments were made, for reasons which will be given in the discussion, using the Burns pneumatic resuscitator. This device (shown schematically in Figure 8) provides intermittent positive pressure respiration of an almost entirely passive kind; it works most satisfactorily when the subject is as completely relaxed as possible, and it has been shown (5) that there is no significant tendency for hyperventilation to occur. It will be seen in Figures 9 and 10 that although there was perhaps a tendency for an initial vasoconstriction to occur when the resuscitator was used, there is no sign of subsequent vasodilation.

Discussion

The data presented in this paper appear to indicate that the decrease in peripheral blood flow observed during pressure breathing by other workers is a transitory phenomenon, succeeded by a slow increase in flow in the majority of normal subjects. We are at a loss for any completely satisfactory explanation of this course of events. The initial decrease in blood flow may signify a period during which the circulation is becoming adapted to the new mechanical conditions imposed by pressure breathing. That is to say, there may be a period in which the volume of circulating blood is reduced, in which the heart is unable to cope with increased pulmonary resistance and in which venous return is significantly impeded. Added to this, there may be a redistribution of blood in the systemic circulation, and indeed it has been shown (3) that constriction of the arterioles occurs in the peripheral vascular bed.

An obvious reason for the succeeding increase in blood flow would lie in an increase in metabolic rate resulting from the increased effort of pressure breathing. It is difficult to estimate in quantitative terms the amount of extra work involved. At first sight it would seem that breathing against constant pressure requires exactly the same amount of work as normal breathing,

the difference consisting merely in the change from active inspiration to passive inspiration and from passive expiration to active expiration. As Fenn and colleagues (4) have pointed out, however, breathing against constant pressure causes a change in the level of respiration, and a change, therefore, in the effective mechanical properties of the lung. Fenn estimates that this change in level of breathing results in a threefold increase of muscular work; the absolute amounts of work involved, however, are not more than 0.1 per cent of the total resting metabolic rate. Thus it seems improbable on these grounds that the increased effort of breathing under positive pressure would be reflected in any measurable change in skin temperature. It is possible, on the other hand, that the efficiency of muscular work in breathing under pressure is so reduced as to give rise to a significant increase in metabolic rate. Increases in oxygen consumption of subjects breathing under positive pressure as great as 10 per cent have been reported, (4) and measurements of our own, while technically unsatisfactory in most cases, likewise suggest that the increased metabolic rate may be considerably greater than the calculated value of 0.1 per cent.

In any event, our data suggest strongly that fears as to the deleterious effects of pressure breathing upon temperature regulation are entirely unfounded.

References

(1) Barach, A. L., Fenn, W. O., Ferris, E. B. and Schmidt, C. F.: The physiology of pressure breathing. A brief review of its present status. Prepared for the Committee on Medical Research, O.S.R.D. December 1944.

(2) Bloom, W. L., Kaufman, S. S., Nims, L. F. and Nyboer, J.: The effect of positive pressure breathing at sea level on peripheral blood flow and cardiac output. C.A.M. Report No. 246. January 1944.

(3) Chadwick, L. E., Fenn, W. O., Hegnauer, A. H., Otis, A. B. and Rahn, H.: Displacement of blood from the lungs during pressure breathing. O.S.R.D., C.M.R., C.A.M. Report No. 249, pages 75-93. December 1943.

(4) Fenn, W. O., Chadwick, L. E., Mullins, L. J., Dern, R. J., Otis, A. B., Blair, H. A., Rahn, H. and Gosselin, R. E.: Physiological effects of pressure breathing. O.S.R.D., C.M.R., C.A.M. Report No. 111. January 1943.

(5) Olson, O. C.: Carbon dioxide elimination. A.A.F., Hq., Air Technical Service Command, Engineering Division, Aero Medical Laboratory., No. TSEAL-3-660-65-D, 15 December 1944.

(6) Sheard, C.: Skin temperatures and thermal regulation of the body. Medical Physics, 1523-1555, The Year Book Publishers, Chicago, 1944.

Effect of Increased Intrapulmonary Pressure on Dark Adaptation

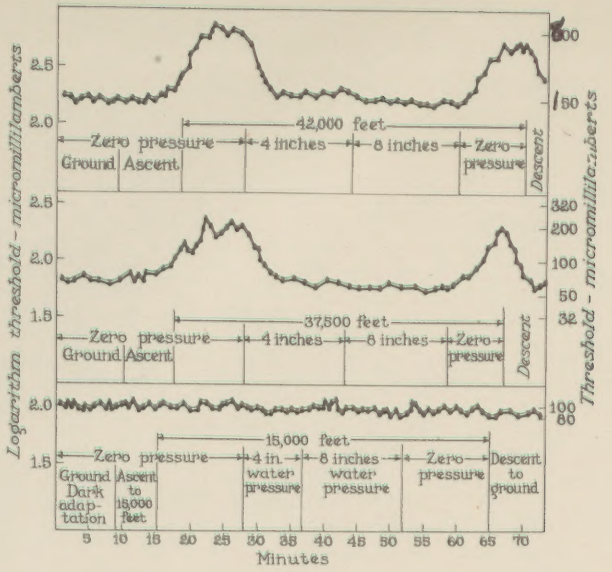

FIG. 1

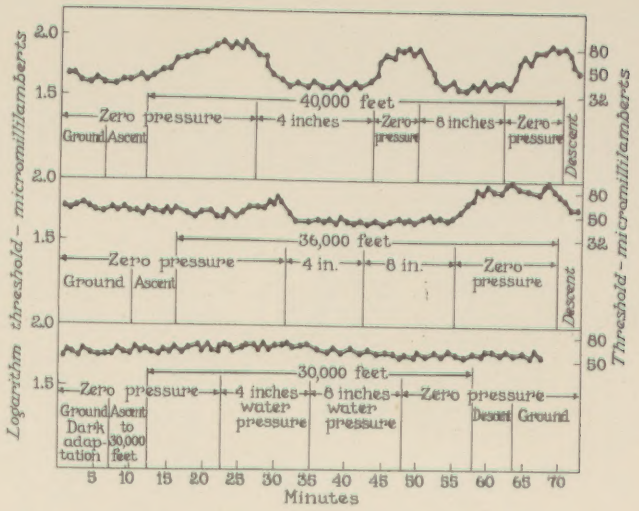

FIG. 2

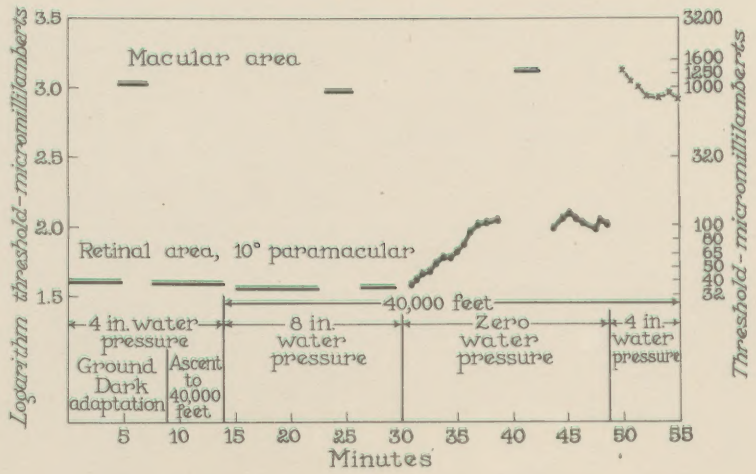

FIG. 3

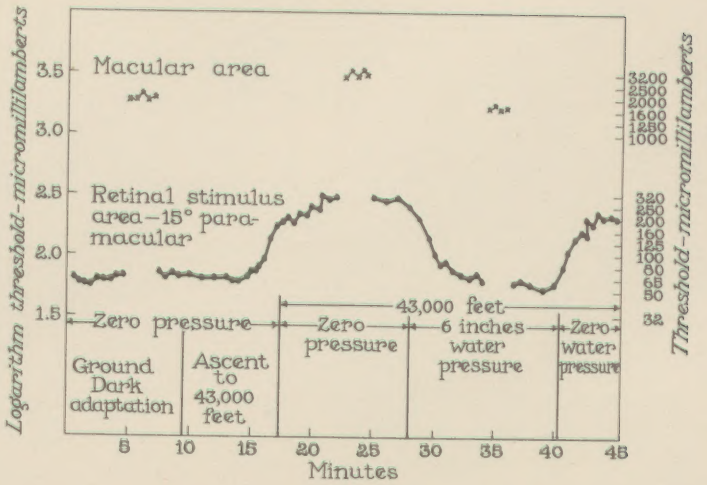

FIG. 4

Chart XVII - 10

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